



Environmental Factor

Your Online Source for NIEHS News

April 2010

NIEHS Spotlight



[House Hearing on Endocrine Disruption](#)

With her most recent testimony, NIEHS/NTP Director Linda Birnbaum, Ph.D., continued her efforts to position the NIEHS as the nation's premier environmental health science authority.



[Birnbaum Gives 2010 Spirit Lecture](#)

To celebrate Women's History Month 2010, NIEHS turned to one of its own to deliver the ninth annual Spirit Lecture presentation — NIEHS/NTP Director Linda Birnbaum, Ph.D.



[Highlights of the 49th Annual SOT Meeting](#)

NIEHS and NTP led the way at the conference with investigators and program officers hosting more than 30 sessions and 60 posters.



[Paules Honored with Leading Edge Award](#)

As far as NIEHS Principal Investigator Rick Paules, Ph.D., is concerned, he wasn't entirely alone on stage when he accepted the SOT 2010 Leading Edge in Basic Science Award.

Science Notebook



[Pesticide Exposure and Child Development](#)

On March 16, epidemiologist and NIEHS grantee Brenda Eskenazi, Ph.D., visited NIEHS to discuss her research with farm workers in California.



[Endocrine Disrupting Compounds and Women's Health](#)

NIEHS and NTP took center stage March 2 on the NIH campus with a seminar sponsored by the NIH Office of Research on Women's Health (ORWH).



[Postdoc Brings Home SOT Awards](#)

NIEHS research fellow Xueqian (Shirley) Wang, Ph.D., received first place prizes for her poster at the annual Society of Toxicology (SOT) Meeting.



[Yale Postdoc Honored for Best Publication](#)

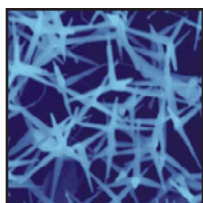
A Yale postdoctoral fellow supported by NIEHS was one of three young scientists honored for Best Postdoctoral Publications at the annual meeting of the Society of Toxicology.

NIEHS Spotlight



[Harry Promotes Exercise at Santa Fe Public Forum](#)

The talk was much more about prevention than basic science when NIEHS Neurotoxicology Group Principal Investigator Jean Harry, Ph.D., spoke March 6 in Santa Fe.



[Revisiting the Concept of "Safe by Design"](#)

In a recent editorial, NIEHS Senior Science Advisor Sally Tinkle, Ph.D., offers a balanced critique of what she describes as "the Holy Grail of Nanotechnology."



[SOT Recognizes Miller with Achievement Award](#)

NIEHS grantee Gary Miller, Ph.D., received the Society of Toxicology (SOT) 2010 Achievement Award for his significant early career contributions to toxicology.



[Birnbaum Puts a Human Face on Climate Change](#)

The real face of climate change is yours and mine, and those of our children, our parents, our friends," said NIEHS/NTP Director Birnbaum, Ph.D., in talk at UNC-CH on March 23.



[Heindel Addresses Pharmaceutical Workshop](#)

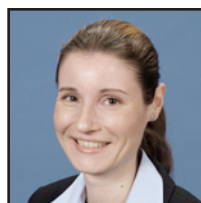
"Pharmaceuticals in the Environment: Lessons Learned" shaped discussion at an all-day workshop that brought together environmental scientists and public policy experts.

Science Notebook



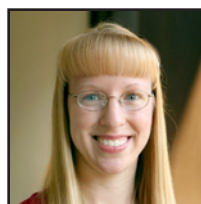
[Study Confirms Link to Lower Risk of Parkinson's](#)

Long-time smokers may suffer more preventable health problems than non-smokers, but their habit can also dramatically lower their risk of developing Parkinson's disease (PD).



[Are We Closer to Effective Treatment for AD?](#)

NIEHS Principal Investigator David Miller, Ph.D., and two of his former postdoctoral fellows have demonstrated a treatment for mice with Alzheimer's Disease.



[Research Offers New Insight into DNA Synthesis](#)

A new NIEHS-funded study challenges current thinking about ribonucleotide incorporation into DNA and may offer new insights into how the human genome is stabilized.



[Regulation and Mutations of Drug Metabolizing Enzymes](#)

NIEHS Principal Investigator Joyce Goldstein, Ph.D., discussed gene expression of a superfamily of drug metabolizing enzymes and the effects of polymorphisms.



[Benefits of Stem Cell Research](#)

NIEHS Principal Investigator Guang Hu, Ph.D, explained how studying embryonic stem cells can lead to a greater understanding of disease mechanisms and lead to advances in gene therapy.

NIEHS Spotlight



[UCSD Documentary Sets the Stage for Change](#)

The border between the United States and Mexico may be fenced, monitored, and patrolled, but that doesn't stop watershed pollution from affecting both sides of the border.



[Collins Honored for Genome Mapping](#)

NIH Director Francis Collins, M.D., Ph.D., is enjoying the honor — but not the cash — for winning a 2010 Albany Prize in Medicine and Biomedical Research.



[Forum to Address Indoor Environmental Exposures](#)

NIEHS/NTP Director Linda Birnbaum, Ph.D., will give the keynote address at a community forum at the Harlem School of the Arts on April 13.



[Biomedical Career Fair Coming April 30](#)

Registration for NIEHS and Environmental Protection Agency (EPA) postdoctoral fellows began March 19 for the 13th Annual NIEHS Biomedical Career Fair.

Science Notebook



[This Month in EHP](#)

French fries on the cover of the April 2010 Environmental Health Perspectives (EHP) could make mouths water — at least until readers digest the story behind the photo.



[Upcoming Distinguished Lecturer Stephen West](#)

The NIEHS Distinguished Lecture Series highlights the links between mutagenesis and cancer with a talk on April 13 by Stephen West, Ph.D.

Extramural Research

[Extramural Papers of the Month](#)

- [Aging Protein Function Revealed](#)
- [Living Near a Major Roadway Linked with Atherosclerosis](#)
- [Blood Type and Pancreatic Cancer Linked](#)
- [African Ancestry and Asthma](#)

Intramural Research

[Intramural Papers of the Month](#)

- [VEGF Rapidly and Reversibly Downregulates P-glycoprotein Activity in the Blood Brain Barrier](#)
- [Threonine-38 Dephosphorylation is Necessary for human CAR Activation](#)
- [Pesticide Use Linked to Thyroid Disease Among Women](#)
- [*Escherichia coli* CysJ Flavin Reductase Detoxifies Mutagenic Nucleobases](#)

Inside the Institute



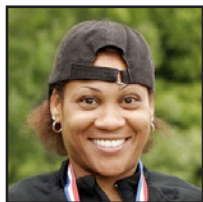
[A Call for National Lab Day Volunteers](#)

NIH Director Francis Collins, M.D., Ph.D., will celebrate National Lab Day (NLD) on the front lines of science education in a Washington, D.C. high school.



[Exploring the History of Women in Science](#)

The NIH Women's History Month Celebration featured two prominent NIH women scientists addressing the topic of "Writing Women into the History of Science."



[Health and Fitness Week Begins May 3](#)

During the first week in May, the annual NIEHS Health and Fitness Week will offer staff a bounty of fun and healthy activities.



[EPA Earth Day Extravaganza to Welcome NIEHS Staff](#)

Organizers of Earth Day events at the U.S. Environmental Protection Agency (EPA) have invited NIEHS staff to join with them in celebrating the 40-year anniversary of Earth Day.

Calendar of Upcoming Events

- **April 12** in Rodbell Auditorium, 2:30–3:30 — Laboratory of Molecular Genetics Fellows Invited Guest Lecturer Martha Bulyk, Ph.D., addressing "Transcription Factor-DNA Interactions: Cis Regulatory Codes in Genomes"
- **April 13** in Rodbell Auditorium, 11:00–12:00 — Distinguished Lecture featuring Stephen West, Ph.D., speaking on "Defective DNA Strand Break Repair and Links to Inheritable Disease"
- **April 13 (Offsite Event)**, at the Harlem School of the Arts in New York City, 2:00–4:00 — Forum on "[Healthy Homes and You](#)," with keynote address by Linda Birnbaum, Ph.D.
- **April 19** in Rodbell Auditorium, 9:00–12:00 — Seminar on Cell Phone Studies with Michael Wyde, Ph.D., and Dariusz Leszczynski, Ph.D.
- **April 20** in Rodbell Auditorium, 10:00–11:00 — Keystone Seminar on "Carcinogenesis: Development Gone Awry," with Ana Soto, M.D., and Carlos Sonnenschein, M.D.
- **April 20 (Offsite Event)**, at Sigma Xi, 12:00–1:00 — James Evans, M.D., Ph.D., director of the UNC Bryson Program in Human Genetics and an advisor to the U.S. Secretary of Health and Human Services on the subject of "Genetics, Health and Society."
- **April 20 (Offsite Event)**, EPA RTP Campus North Surface Lot, 11:00–3:00 — Green Vendor Fair
- **April 21 (Offsite Event)**, EPA RTP Campus C Plaza and C111 auditorium, 8:30 – 10:30 — Fun Run and speech by Hunter Lovins, author and founder of Natural Capitalism Solutions
- **April 21** in Rodbell Auditorium, 6:00–8:00 p.m. — Seminar on Graduate Women in Science, "Life After the Post-Doc Part Deux"
- **April 22 (Offsite Event)**, EPA RTP Campus C Plaza — Speech by Robert F. Kennedy Jr.
- **April 26-27** in Rodbell Auditorium, 8:00–5:00 — Partnerships for Environmental Public Health Inaugural Meeting
- **April 29** in Keystone 1003AB, 11:00–12:00 — Keystone Lecture Series with Francesca Dominici, Ph.D., topic TBA
- **April 30 (Offsite Event)**, EPA RTP Campus Conference Center, 8:30–4:30 — [NIEHS Biomedical Career Fair](#)
- View More Events: [NIEHS Public Calendar](#)

House Hearing on Endocrine Disruption

By Eddy Ball

With her most recent Congressional testimony, NIEHS/NTP Director Linda Birnbaum, Ph.D., continued her efforts to position the Institute as the nation's premier environmental health science authority. In the past four months alone, Birnbaum has testified before four Congressional hearings investigating the safety and environmental health impact of chemicals.

On Feb. 25, Birnbaum presented oral and [written testimony](#) to the [U.S House of Representatives Committee on Energy and Commerce Subcommittee on Energy and Environment](#) chaired by Rep. Edward Markey (D-Mass.) addressing “Endocrine Disrupting Chemicals in Drinking Water: Risks to Human Health and the Environment.” Her testimony underscored the threats to health posed by increasing exposures to endocrine disrupting chemicals (EDCs) and the pressing need to create “effective strategies to ensure safe drinking water and the health of the American public.”

Markey opened the hearing by describing the rising concern among citizens about the poorly understood health effects of exposures to chemicals that interfere with, or mimic, hormones in the human body. “W.C. Fields once said, ‘I never drink water because of the disgusting things that the fish are doing to it,’” Markey observed. “Today people are wondering whether they should drink water that comes out of their taps because of the disgusting things it is doing to the fish — and possibly to them.”

Birnbaum opened her five-minute testimony with a statement of the Institute's longstanding interest in EDCs, which she said goes back to the establishment of NIEHS in the 1960s, and presented an overview of the directions of recent research by NIEHS and NTP. She also pointed to four reasons why researchers have concerns about EDC exposures:

- Low doses matter — “Some chemical exposures, even at low doses, may disrupt the body's delicate endocrine system and lead to disease.”
- There is a broad range of health impacts — “When chemicals interfere with endocrine signaling, effects can be seen in many different conditions and diseases.”
- Exposure during development can trigger changes in gene expression — “The health effects of exposure to endocrine disruptors can be observed long after the actual exposure has stopped” and may even result in alterations among members of succeeding generations.



COMMITTEE ON ENERGY AND COMMERCE



*In addition to her testimony on children's environmental health and her most recent appearance Feb. 25, Birnbaum testified on reform of the Toxic Substances Control Act (TSCA) on [Dec. 2, 2009](#) and [Feb. 4, 2010](#). Birnbaum reflected on her TSCA testimony in an [editorial](#) in the March issue of *Environmental Health Perspectives*. (Photo courtesy of Steve McCaw)*

- EDCs can be found almost everywhere —
“Chemicals with endocrine disrupting activity are widely dispersed in our environment, often at biologically effective levels, and exposure to humans is common.”

Also testifying before the subcommittee on Feb. 25 were Jim Jones, deputy assistant administrator, Office of Prevention, Pesticides and Toxic Substances at the U.S. Environmental Protection Agency; Gina Solomon, M.D., M.P.H., senior scientist at the Natural Resources Defense Council; and Christopher J. Borgert, Ph.D., president and principal scientist at Applied Pharmacology and Toxicology, Inc.

[Return to Table of Contents](#)



Markey, shown above at 2008 hearing on global warming, is sponsoring a bill to ban bisphenol A from food and beverage containers and has expressed his concerns about the use of anti-microbials, such as triclosan (see [story](#)). (Photo courtesy of U.S. House of Representatives)

Birnbaum Gives 2010 Spirit Lecture

By Eddy Ball

To celebrate Women’s History Month 2010, NIEHS turned to one of its own to deliver the ninth annual Spirit Lecture presentation — NIEHS/NTP Director [Linda Birnbaum, Ph.D.](#) Birnbaum spoke to a near-capacity audience on March 26 about her life and her work during an afternoon presentation titled “You Can Have It All,” co-sponsored by the NIEHS Diversity Council (DC) and the Women Scientists Assembly (WSA).

NTP Toxicologist and DC Spirit Lecture Committee Chair Molly Vallant opened the proceedings with a welcome to employees and visitors to the event, reminding them of the history of the Spirit Lecture series and its theme of balancing self, work, and family. NIEHS Staff Scientist Leesa Deterding, Ph.D., WSA co-chair, then introduced Birnbaum and spoke briefly of her colleague’s success in achieving satisfaction in, and harmony among, the various aspects of her life.

A quest for passion and balance

“What for me is synonymous with ‘spirit’ is fun,” Birnbaum said, as she opened her talk with the theme that would inform her presentation. “I’ve always done things that I enjoy, fulfilling my love of science, keeping involved with the community, and of course my family.”

Describing her life as a teenager and young adult, Birnbaum recalled her parents’ support for her early scientific interest and her desire to pursue graduate degrees during a time when “there weren’t a lot of women in the sciences.” She reflected on her passion for the love of her life, for her profession, and for her family, as well as the challenge of making time for the important things in life — even when that meant putting her career on hold temporarily.



As she spoke of faith and family, of community and career, Birnbaum paused to glance fondly at photos projected on the screen in Rodbell Auditorium and webcast throughout the Institute and to employees in Bethesda. (Photo courtesy of Steve McCaw)

“My family is always first,” she said. “Maybe I could have done something differently — worked harder and gotten here five years sooner — but who cares? So what?”

Along with valuing balance and flexibility, Birnbaum called on her listeners to “follow your nose” — to take advantage of opportunities as they arise and understand when to take new directions in life. She pointed to her own progression of “moving up the phylogenetic ladder” from microbiology and biochemistry to toxicology and scientific leadership, as she matured in her professional life.

“Enjoy what you do with a passion,” Birnbaum told her audience. Surround everything you do with passion, and life turns out pretty good. If you’re not having fun, you’d better be doing something else.”

Addressing the work at hand

With the same level of energy and enthusiasm she brought to her personal narrative, Birnbaum turned to her work as NIEHS/NTP director pursuing improvements in public health locally, nationally, and globally. She described the Institute’s successes and ongoing efforts to raise “awareness of the linkages between the environment and health” and to help scientists and citizens “think [more carefully and consistently] about research from a multi-stakeholder perspective.”

Birnbaum outlined NIEHS and NTP environmental public health initiatives to increase understanding of the long-range effects of early exposure to chemicals and pointed to advances in personal monitoring and remote sensing technologies. With the results of ongoing environmental health science research, she said, “We have the opportunity to increase awareness of the changes in a chemical or material during manufacture, use, and disposal.” She added that understanding “changes that could impact human exposure, uptake, and biological effect” could have important implications for the development of primary prevention measures to address complex diseases triggered by complex exposures.

As she concluded her presentation, Birnbaum spoke with pride of the Institute’s accomplishments and promise for the future. “Things are looking very good for us right now,” she observed. “When an expert is needed, [legislators, stakeholders, and decision makers are] coming to us first, and that speaks to how we’re positioned” to shape the direction and lexicon of public health discourse.



Like others in the audience, NIEHS Biologist Wendy Jefferson, Ph.D., center, enjoyed Birnbaum’s keen sense of the ridiculous as she described 1960’s perceptions of the role of women in education and the workplace. Sitting with Jefferson is Postdoctoral Fellow Minerva Mercado-Feliciano, Ph.D. (Photo courtesy of Steve McCaw)



Birnbaum, left, smiled as she received her Spirit Lecture plaque from host Vallant. Not shown are DC Chair Brad Collins and member Angela King-Herbert, D.V.M., who also joined Birnbaum at the podium. (Photo courtesy of Steve McCaw)



As employees and visitors enjoyed refreshments, NTP Geneticist Jack Bishop, Ph.D., left, chatted with NIEHS Principal Investigator Mike Resnick, Ph.D. (Photo courtesy of Steve McCaw)



Following her talk, Birnbaum posed beside the poster advertising her talk. (Photo courtesy of Steve McCaw)



Members of the DC and WSA gathered for a group photo during the reception following the talk. Show above, left to right, are King-Herbert, Vallant, Diane Spencer, Birnbaum, WSA Co-chair Michelle Hooth, Ph.D., Collins, Helen Cunny, Ph.D., and Veronica Godfrey Robinson. (Photo courtesy of Steve McCaw)

Highlights of the 49th Annual SOT Meeting

By Ed Kang

Leading toxicologists and environmental health scientists shared their latest findings, discussed funding and training opportunities, received input on future research priorities, and more at this year's Society of Toxicology (SOT) meeting in Salt Lake City. NIEHS and NTP led the way at the 49th annual SOT conference with investigators and program officers hosting more than 30 sessions and 60 posters.

Among the highlights of this year's conference were the [Live Updates](#) provided by attendees. NIEHS and NTP representatives, including Director Linda Birnbaum, Ph.D., and guests, such as Cheryl Walker, Ph.D., outgoing president of SOT and an NIEHS [grantee](#), posted nearly 100 real-time updates. These unscripted postings, viewable in a day-by-day account, gave web viewers a unique "behind the scenes" perspective of the conference.



Nadadur, third from left, posed with colleagues from other groups and institutions who shared his interests in the promise of new technologies. Shown, left to right, are Kevin Dreher, Ph.D., Arun Sreekumar, Ph.D., Nadadur, Steve Hamilton, M.D., Ph.D., Mary Jane Cunningham, Ph.D., and Steve Belinski, Ph.D. (Photo courtesy of Ed Kang)

Next year's meeting is the Society's 50th and will be held in Washington, D.C. It promises to be a spectacular event with more of what makes this gathering of the toxicology community such an amazing experience.

Some of the highlights about NIEHS scientists at the 2010 conference:

- **[A View from the Top](#)** — Birnbaum recapped the Institute's successes for the past year and her thoughts for the future. She talked about the link between environmental health and prevention, and the connection between bench, policy, and public health.
- **[Promises, Pitfalls and the Potential of High Throughput Technologies](#)** — Sri Nadadur, Ph.D., co-chaired a discussion of technologies to better understand toxic responses and for generating global molecular profiles.
- **[The Best of Toxicology](#)** — [SOT] recognized some of the very best in our profession: Mike Waalkes was elected to the SOT Council, and Rick Paules, Ph.D., was awarded the Leading Edge in Basic Science Award for his contributions to understanding fundamental mechanisms of toxicology (see related [story](#)).
- **[The Future of Toxicology](#)** — Students were able to enjoy an opportunity to network with professionals. A panel of experts including NTP Toxicologist Michelle Hooth, Ph.D., spoke to 200 students about opportunities, successes and lessons-learned. Hooth also co-chaired a collaborative informational [session](#) on tungsten and tungsten alloys.
- **[Herbals and Women's Health Discussion](#)** — Nigel Walker, Ph.D., of NTP, reviewed dietary supplements, with Retha Newbold, recently retired from NIEHS, speaking on developmental exposure, and Mark Cline, D.V.M., Ph.D., of Wake Forest University speaking on adult exposure to soy.
- **[Immunotox Specialty Section Celebrates Its Silver Jubilee](#)** — The Immunotox Specialty Section celebrated 25 years at SOT. The highlight of the event was the "Paper of the Year" award won by a project funded by an NTP-NIOSH interagency agreement.

- **Organize It and They Will Come** — Ray Tice, Ph.D., of NTP, and Bob Kavlock, Ph.D., of EPA, organized “The Tox21 Community and the Future of Toxicology.” Related presentations included efforts to develop a 10,000 compound library for testing by Cynthia Smith, Ph.D., and insights into the future of toxicology from Birnbaum.



Hooth, with microphone, talked with aspiring members of the next generation of toxicologists about the future of the discipline. (Photo courtesy of Ed Kang)



Birnbaum, left, is shown with one of the many people she talked with about one of her favorite topics — the importance of NIEHS efforts in the quest to improve public health. (Photo courtesy of Ed Kang)

These and many other updates are available through the end of April at <http://tools.niehs.nih.gov/blog/sot/>.

(Ed Kang is a public affairs specialist in the Office of Communications and Public Liaison and a regular contributor to the Environmental Factor.)

[Return to Table of Contents](#)

Paules Honored with Leading Edge Award

By Eddy Ball

As far as NIEHS Principal Investigator [Richard Paules, Ph.D.](#), is concerned, he wasn't entirely alone on stage when he accepted the 2010 Leading Edge in Basic Science Award at the Society of Toxicology (SOT) Annual Meeting March 7-11 in Salt Lake City. Although he was the individual singled out for the honor, Paules felt the presence there of the many friends and colleagues who have worked to advance the field of toxicogenomics (see [text box](#)) and predictive toxicology over the past 15 years.

Paules credits collaborations, community, and consortia

“I feel honored to receive the award for the Institute,” said Paules, who heads the Environmental Stress and Cancer Group and directs the Microarray Core Facility at NIEHS. “There have been a huge number of people who have contributed significantly to the development of toxicogenomics here at NIEHS, and I felt that I was a representative for all of those people.”



Speaking of the translational impact of toxicogenomics, Paules said, “There are very clear applications in the present and near future that are incremental steps, such as fit-for-use purposes in the clinical setting.” He mentioned specifically predictive tests for preventing and treating liver damage well before it shows up on the clinical chemistry tests currently used. (Photo courtesy of Ed Kang)

Paules pointed to colleagues from the intramural program and grantees in the National Center for Toxicogenomics (NCT), postdoctoral fellows in the several labs involved, and scientists in the National Toxicology Program, as well as the inspired leadership of former Director Ken Olden, Ph.D.

SOT underscores Paules' leadership and innovation

Recognizing Paules “for his work in the integration of genomics into the investigation of the molecular basis of injury and disease processes,” the award committee described him as “a visionary ... who has diligently positioned NIEHS at the forefront of the field.” The commendation recognized Paules for his administrative and scientific leadership and his advocacy of the development of publicly accessible databases to facilitate discovery research using ‘omics methodologies.

The awards committee emphasized the importance of Paules' leading edge proof-of-concept studies in the development of predictive biomarkers of the initiation and progression of those processes.

Building on successes and looking ahead

As part of his honor, Paules presented an award lecture on “Toxicogenomics at NIEHS: How Genomics Is Impacting the Science of Toxicology.” He reflected on the “big-science” team approach to addressing the challenges of applying ‘omics technologies, including “technical problems associated with gene annotation and platform development, detection of true signals, bioinformatic determination of significant changes, and reliability across different platforms and different users.”

“While the challenges [of developing signatures to utilize as clinical biomarkers of specific adverse effects] are great,” Paules concluded, “the prospects have never been brighter.”

“I really hope to provide better science for better treatment of disease,” Paules said as he looked toward the future. “There’s a huge need to put better information in the hands of clinicians, and I think genomics is an important tool for helping us reach that goal.”

[Return to Table of Contents](#)

Defining “Toxicogenomics”

Environmental toxicogenomics is an approach to environmental toxicology that allows researchers to identify and characterize genomic signatures of environmental toxicants as gene and protein expression profiles as well as metabolite profiles. A major application of gene expression profiling is to understand human genetic variability and susceptibility to adverse exposures and to disease development and progression.

Program Goals

- To facilitate the application of genome-wide gene and protein expression technology to toxicology
- To understand the relationship between environmental exposures and human disease susceptibility
- To identify useful biomarkers of disease and exposure to toxic substances
- To improve computational methods for understanding the biological consequences of and responses to exposure
- To create a public database of environmental effects of toxic substances in biological systems

Harry Promotes Exercise at Santa Fe Public Forum

By Eddy Ball

The talk was much more about prevention than basic science when NIEHS Neurotoxicology Group Principal Investigator [Jean Harry, Ph.D.](#), spoke March 6 at a public forum in Santa Fe, N.M. Harry discussed the “Protective Mechanisms of Exercise: Running to Win” at the evening forum — a public service and outreach effort on the part of scientists attending the [41st annual American Society for Neurochemistry \(ASN\) meeting](#) held there March 6-10 that attracted some 230 attendees from the Santa Fe area.

The theme of the ASN Public Forum was “Nutrition, Exercise and Dietary Supplements: Impact on Physical Health and Brain Function.” In her talk on exercise, health, and brain function as people age, Harry focused on the benefits of protection from environmental exposure to neurotoxicants and exercise, with regard to increasing brain health and brain repair, as strategies for preventing or delaying onset of Parkinson’s, Alzheimer’s, and other neurodegenerative diseases.

Harry’s keynote talk was learned, but informal. While she steered away from her specialized breakthrough studies on the role of microglia in brain inflammation linked to neurodegenerative diseases, Harry did integrate new data as evidence of solid scientific support for the benefits of exercise in preventing and moderating developmental and adolescent neurological disorders.

Following Harry at the podium were Loyola University Chicago nutritional biochemist [Susan McGuire, Ph.D.](#), and Tufts University nutrition researcher [James Joseph, Ph.D.](#) McGuire addressed regulatory issues in her talk on “Dietary Supplements: Good, Bad or Ugly?” and Joseph explored the question “Fruits, Nuts and Brain Aging: Do the Forest Animals Have it Right?”

Santa Fe area registered dietitians Jan Esparza, Nina Dougherty and Kelle Vort joined the speakers in a panel discussion following the talks, giving members of the audience an opportunity to air concerns about their health and ask advice for laying the foundation of healthy aging by adopting positive lifestyle changes.



Harry, who exercises regularly herself, proved to be a good role model, as well as science educator, for the people who attended the ASN Public Forum. (Photo courtesy of Steve McCaw)



Harry, second from left, looks on with other panelists as Joseph makes a point about the benefits of grape juice, berries, and walnuts on brain aging and behavior. (Photo courtesy of Jean Harry)

[Return to Table of Contents](#)

Revisiting the Concept of “Safe by Design”

By Eddy Ball

In her recent editorial for the Web site Azonanotechnology, NIEHS Senior Science Advisor Sally Tinkle, Ph.D., offers a balanced critique of what she describes as “the Holy Grail of Nanotechnology” as she examines the assumptions behind the concept of Safe by Design (SxD).

As Tinkle explains in her [article](#), however intriguing SxD may be as a concept, it also presents several fundamental challenges for scientists. According to her, scientists still don’t understand the wide range of variables that determine how elements behave well enough to determine whether SxD can actually be a feasible strategy for achieving product safety while maintaining the beneficial properties of ENMs, as the sizes, electrical charges, surface coatings, and shapes of elements are altered to produce engineered [nanomaterials](#) (ENMs).

Like the Holy Grail’s promise of salvation, the promise of SxD remains enticingly out of reach, according to Tinkle.

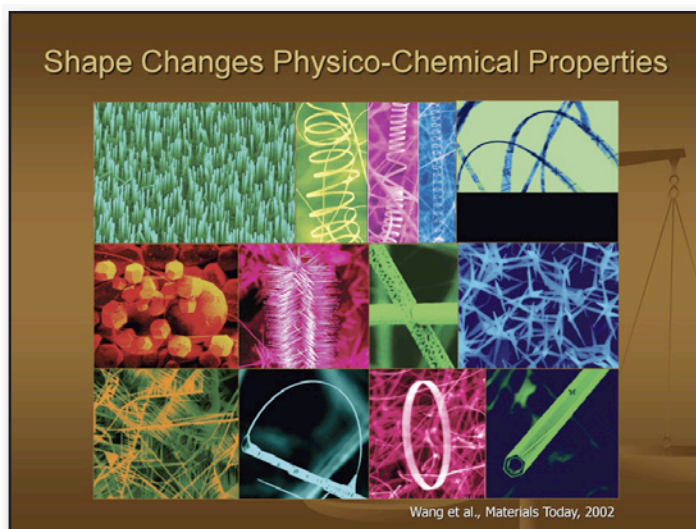
Tinkle’s caveats parallel [concerns](#) expressed by NTP scientists Nigel Walker, Ph.D., and John Bucher, Ph.D., in a paper last year on applying a next-generation systematic biological-pathways testing approach to risk analysis of ENMs. Walker and Bucher pointed to the variability among products in terms of physical qualities, manufacturing practices, and microenvironmental interactions as reasons that high-throughput methods may not be appropriate for testing many ENMs.

Not surprisingly, Tinkle thinks “it’s time to step back and re-examine what we’ve been saying [about SxD] with some research that asks the necessary questions, so we could perform meta-analysis on the data from those studies to take us in the direction we want to go.” Tinkle added that NIEHS has taken the lead in funding research “to see how precisely we can identify the subset of physical and chemical properties of a material and relate them to biological response.”

Even if scientists can discover systematic principles that govern the often contradictory behaviors of the broad spectrum of nanomaterials, Tinkle added, SxD may not be the most cost-effective approach for protecting public health. In the end, the most feasible approach may yet prove to be a time-consuming product-by-product approach to risk analysis and safety engineering similar to the one used in conventional toxicology.



Tinkle describes SxD efforts as “a balancing act between benefit and risk.” Tinkle cautioned that ENMs may be “so exquisitely sensitive” that engineering for safety could also alter their beneficial properties. (Photo courtesy of Steve McCaw)



This slide from a presentation by Tinkle illustrates the range of shapes found in ENMs. Changes in shape, she explains, alter the products’ physical and chemical properties in ways that impact their potential effects on human health. (Graphic courtesy of Sally Tinkle)

Teasing out the Implications of SxD

Tinkle looked at three as yet unsubstantiated assumptions behind the concept of SxD:

- That there exist subsets of physical and chemical properties, which consistently produce the same biological response in multiple microenvironments
- That scientists will be able to isolate the physical and chemical properties that trigger individual adverse biological reactions that may affect an organism from the exponential number of combinations of physical and chemical properties possible for ENMs
- That designers can maintain the beneficial properties of an ENM, such as targeted drug delivery, while engineering out those that cause an adverse effect

In support of the plausibility of SxD, Tinkle points to recent findings about what is called the “corona,” a limited number of proteins that bind to the surface an ENM. “Because the number of proteins that bind to the surface of the material is more limited,” Tinkle explained, “it may be that these proteins limit the biological responses than can occur.”

[Return to Table of Contents](#)

SOT Recognizes Miller with Achievement Award

By Eddy Ball

During the Society of Toxicology (SOT) annual meeting in Salt Lake City, March 7-11, NIEHS grantee Gary Miller, Ph.D., received the group’s 2010 Achievement Award for his significant early career contributions to toxicology.

Miller is a professor in the Department of Environmental and Occupational Health and associate dean for research in the Rollins School of Public Health at Emory University. He serves as the principal investigator on NIEHS grants for the [Emory Parkinson’s Disease Collaborative Environmental Research Center](#), [Graduate and Postdoctoral Training in Toxicology](#), and [Neurotoxicity of Nanomaterials: Evaluation of Subcellular Redox State](#).



Principal investigator Gary Miller is shown in his laboratory at Emory. (Photo courtesy of Ann Borden, Emory University)

SOT praised Miller for his “top-notch toxicological research in the field of neuroscience” with his investigations into the environmental and genetic factors involved in neurological disease — particularly the role of pesticides in the development of Parkinson’s disease (see [story](#)). Miller and colleagues presented an overview of their research program in October 2009 at the first annual meeting of the NIEHS Centers for Neurodegeneration Science (see [story](#)).

Overseeing Miller’s grants in the NIEHS Cellular, Organ, and Systems Pathobiology Branch are Health Science Administrators Cindy Lawler, Ph.D., Sri Nadadur, Ph.D., and Carol Shreffler, Ph.D.

[Return to Table of Contents](#)

Birnbaum Puts a Human Face on Climate Change

By Robin Mackar

The first slide in a presentation by NIEHS/NTP Director [Linda Birnbaum, Ph.D.](#), before an audience of more than 100 college students, professors, and concerned citizens was of a cuddly, vulnerable-looking polar bear. “This is not the face of climate change we’re going to be talking about tonight,” said NIEHS/NTP Director Linda Birnbaum, Ph.D., as she began her March 23, 2010

evening climate change talk at the University of North Carolina at Chapel Hill (UNC-CH) [Institute for the Environment](#) ongoing Environmental Seminar Series, which was co-sponsored by the [UNC Gillings School of Global Public Health](#).

“The real face of climate change is yours and mine, and those of our children, our parents, our friends — everyone we care about, and all of our fellow humankind,” Birnbaum said as she showed a series of captivating slides depicting the human faces of climate change — including a woman whose home was destroyed by fire, another’s destroyed by Hurricane Katrina, a young boy using an inhaler, a newborn, and a man overwhelmed by the heat in the city. “The consequences of climate change on people are just as real as the effects on polar bears and other wildlife.”

Summarizing some of the key points scientists have recently learned about how the earth’s climate is changing or expected to change in coming years, Birnbaum said scientific consensus shows that temperatures are in fact rising, and have been accelerating over the past 60 years. The Intergovernmental Panel on Climate Change predicts average temperatures to increase by anywhere from about 1.5 degrees to 6 or 7 degrees centigrade by the beginning of next century, she added, noting the dramatic and well-publicized effects of climate change on the natural landscape, such as diminishing ice masses in places like the Mount Kilimanjaro and changes in sea levels. Birnbaum also discussed in detail how climate is affecting human health and what research is needed to address its impact (see [text box](#)).

Birnbaum then turned to reasons for hope. “The good news is, we have many of the skills, expertise, and tools we already need to achieve major public health benefits while avoiding some of the worst human consequences of climate change in our communities.” She highlighted efforts by NIEHS, the U.K.’s Wellcome Trust, the London School of Hygiene and Tropical Medicine, and several others to co-fund a set of studies looking at what the effects for health might be with some fairly technologically simple changes. The papers were published in the journal *The Lancet* in November 2009 and highlighted by press conferences in both the U.S. and U.K. (access links to papers and National Press Club video [online](#))

Birnbaum concluded her presentation by highlighting the role that NIEHS is playing to help mitigate the effects of climate change, including NIEHS’s recent support of several American Recovery and Reinvestment Act grants related to climate change, the addition of physician John Balbus who will serve as the Institute’s



Birnbaum, who is also an adjunct professor at UNC-CH, easily established rapport with her academic audience, as she called for community support in the quest to ameliorate the effects of climate change. (Photo courtesy of Steve McCaw)

senior advisor for public health (see [story](#)), overseeing NIEHS efforts on climate change and health, and she also highlighted several of the interagency efforts NIEHS is leading or participating in.

Birnbaum then reached out to UNC-CH and others in the public health community to join NIEHS and federal agencies in their efforts to address climate change. “Humans are the only species that can work to undo this damage and protect our planet and our health. It will take the combined intellect, will, and resources of all of us to do this, but it can be done. And the time to start is now.”

(Robin Mackar is the news director in the NIEHS Office of Communications and Public Liaison and a regular contributor to the Environmental Factor.)

Climate Change Research Priorities

During her talk, Birnbaum focused on eight disease areas that have been identified by NIEHS and other agencies in a soon to be released white paper as being impacted by climate change and that need to be addressed through further research. These included:

- Respiratory allergies and airway diseases
- Cardiovascular diseases and stroke
- Food-borne disease and nutrition
- Heat-related morbidity and mortality
- Mental health and stress-related disorders
- Vector-borne and zoonotic diseases
- Water-borne diseases
- Weather-related morbidity and mortality

[Return to Table of Contents](#)

Heindel Addresses Pharmaceutical Workshop

By Thaddeus Schug

“Pharmaceuticals in the Environment: Lessons Learned” shaped discussion at an all-day [workshop](#) that brought together environmental scientists and public policy experts February 27 at the University of Guelph in Ontario, Canada. [Jerry Heindel, Ph.D.](#), a program administrator and acting branch chief in the NIEHS Division of Extramural Research and Training (DERT), joined participants in discussions involving pharmaceuticals and endocrine-disrupting chemicals (EDCs) in the environment and research and policy on new chemicals.

According to conference organizers, few pharmaceuticals are present in high enough amounts in the environment to harm aquatic plants and animals. But growing public concern has led policymakers to focus on these products at the expense of addressing risks posed by new chemicals — so-called “chemicals of concern” — such as flame retardants, nanomaterials, and chemical mixtures. The workshop was geared at addressing the public misconceptions and controversy surrounding EDCs.

Heindel’s presentation focused on chemical exposures during the early developmental stages of life. According to Heindel, “many



Heindel is the administrator of a new ARRA-funded Grand Opportunities (GO) initiative on the EDC bisphenol A (BPA) that aims to foster productive collaborations and platform compatibility in investigations into effects of the chemical on human development. (Photo courtesy of Steve McCaw)

pharmaceuticals, pesticides, and industrial chemicals are found in low levels in our environment, but even at low concentrations they may have human health effects. Low dose chemical exposures during a critical window of susceptibility — *in utero* through the first few years of life — can cause permanent damage to developing tissue.” He added that more research is needed to determine when levels of pharmaceuticals become dangers to human health.

Epigenetic alterations may last a lifetime — and beyond

Heindel said that multiple factors, such as the type and dose of chemicals, the timing of exposure, and the genetic make-up of an individual, all contribute to disease etiology. “Even at very low doses, multiple exposures of single chemicals or chemical mixtures, during windows of development, may alter epigenetic programming that lasts a lifetime.”

Heindel explained that exposure-induced epigenetic modifications are creating a shift in toxicology ideology. He posed the question, “How can environmental chemicals cause effects long after the exposure?” He explained that genes are turned on and off in temporal patterns during development, and that EDCs can modify DNA and histones at these critical junctures. These changes in DNA methylation or chromatin modifications persist throughout life and can result in altered gene expression, which can then lead to the development of diseases long after the environmental chemical exposure is over.

Low doses of EDCs add up

Heindel used arsenic exposure, examined in experiments published by Michael Waalkes, Ph.D., of NIEHS, to illustrate the importance of chemical dosage during development. While tolerable in adult mice, doses as low as 24-84 parts per million (ppm) during gestation have been shown to lead to multiple forms of cancer. A recent study also demonstrated that multiple doses as low as 6 ppm over a lifetime resulted in high rates of tumor formation, indicating that animals are more sensitive to a combination of developmental and lifetime exposures than to developmental exposures alone.

Heindel concluded that these examples raise the question of whether low dose environmental exposure to certain chemicals might be at the origin of other diseases such as obesity. He showed examples of environmental chemicals called “obesogens” that have been shown to cause weight gain in rodent models and proposed that this might be just the tip of the iceberg.

(Thaddeus Schug, Ph.D., is a postdoctoral research fellow in the NIEHS Laboratory of Signal Transduction.)

Pharmaceuticals in the Environment: Lessons Learned

February 27, 2010, University of Guelph, Canada

Workshop Presenters:

- Jerry Heindel, Ph.D., NIEHS, Pharmaceuticals in the Environment
- Judith McKenzie, Ph.D., University of Guelph, The Effects of Pharmaceutical Contaminants on the Health of Women and Children
- Karen Kidd, Ph.D., University of New Brunswick, Fish Contraception
- Vance Trudeau, Ph.D., University of Ottawa, Effects of Pharmaceuticals on Sex Hormones in Aquatic Animals
- Bryan Brooks, Ph.D., Baylor University, Water Quality and Chemicals of Concern
- Lynn Frewer, Ph.D., Wageningen University, Public Perceptions of Risk

[Return to Table of Contents](#)

UCSD Documentary Sets the Stage for Change

By Rebecca Wilson

The border between the United States and Mexico may be fenced, monitored, and patrolled, but that doesn't stop watershed pollution from affecting both sides of the border. University of California-San Diego (UCSD) Superfund Research Program (SRP) researcher and NIEHS SRP [grantee](#) Keith Pezzoli, Ph.D., is trying to change that. His efforts are chronicled in the new documentary "Los Laureles Canyon: Research in Action," which airs on UCSD-TV and was screened at a symposium at the American Association for the Advancement of Science (AAAS) Annual Meeting on February 22 (watch [video](#)).

[Pezzoli](#) is engaging fellow researchers, community and tribal leaders, and government officials from both countries in a "scholarship of engagement." The goal is to remediate the area's waters and create a sustainable community for the 65,000 inhabitants of the Los Laureles Canyon living near the border in Tijuana.

Cooperative efforts such as the one documented in the film are essential, according to Pezzoli. "A lot of the development in the world over the next 30 years will be like this," he said. He pointed to benefits for scientific research, as well. "We are testing soil for contaminants using Superfund research technology. We're bringing advanced techniques into the field to get a better grasp on pollution."

The film grew out of a tour that Pezzoli and environmental research scientist [Hiram Sarabia](#) conducted as part of the American Public Health Association (APHA) 2008 Annual Meeting, a [story](#) featured in the February 2009 edition of the Environmental Factor. The final result, produced with the help of UCSD-TV, follows researchers, students, and community members in their quest to find solutions for the Los Laureles Canyon settlement.

The canyon's growing population, challenged with poverty and poor sanitation, places a significant environmental burden on the Tijuana Estuary in California. Untreated wastewater, erosion, and heavy metals, such as zinc, copper, and lead, clog and pollute the estuary waters, which provide a home to migratory birds and butterflies. According to Pezzoli, the United States currently spends \$1.5 million every year clearing sediment and pollutants out of this estuary on the U.S. side of the border so the water may flow into the Pacific Ocean.



The Los Laureles Canyon, home to 65,000 residents, is upstream from a sensitive estuary that straddles the border between the United States and Mexico. Erosion and poor sanitation contribute to environmental and human health problems alike. (Photo courtesy of UCSD)



UCSD students work with residents to build pervious concrete brick in a local schoolyard. Efforts to streamline the process have resulted in jobs for the residents and the promise of improvement in the community. (Photo courtesy of UCSD)

After exploring the scope of problems in the border area, the film then documents one example of possible solutions. Pezzoli and Sarabia travel down to the canyon with a team of students and show the residents how to build roads made of pervious concrete. Closely resembling a honeycomb made of popcorn, pervious concrete roads allow water to run through them and into the estuary downstream. The roads improve health by reducing the dust produced as a result of driving, and they act as a barrier to further erosion.

Though it is a small act, these activities have a major impact on the lives of the residents. The students were able to make about 700 tiles of pervious concrete; but to make a significant impact, the residents of the canyon need 100 times that amount. The [National Oceanographic and Atmospheric Administration \(NOAA\) Coastal Training Program](#) coordinator for the estuary, Oscar Romo, has been working with residents to streamline the process. This has an additional benefit — the creation of jobs for the residents, with a final product that benefits the community.

UCSD-TV is translating the film into Spanish and will be available later in the year.

(Rebecca Wilson is an environmental health information specialist for MDB, Inc., a contractor for the NIEHS Superfund Research Program and Worker Education and Training Program.)

[Return to Table of Contents](#)

Collins Honored for Genome Mapping

By Eddy Ball

NIH Director [Francis Collins, M.D., Ph.D.](#), is enjoying the honor — but not the cash — for winning a 2010 Albany Medical Center Prize in Medicine and Biomedical Research. In its March 10 announcement, Albany Medical College named this year's winners, which include David Botstein, Ph.D., of Princeton University, and Eric Steven Lander, Ph.D., of Harvard Medical School, in addition to Collins, who was honored for his leading role in mapping the human genome.

Awarded annually, the \$500,000 [prize](#) is the largest prize in medicine in the United States and is bestowed on any physician or scientist, or group, whose work has led to significant advances in the fields of health care and scientific research with demonstrated translational benefits applied to improved patient care, according to the Albany Medical College Web site. A message from the NIH Office of the Director explained that Collins declined his portion of the \$500,000 prize in order to comply with government ethics rules.

In addition to his most recent honor, Collins is an elected member of the Institute of Medicine and the National Academy of Sciences. He was awarded the Presidential Medal of Freedom in 2007. In a White House ceremony on Oct. 7, 2009, Collins received the National Medal of Science, the highest honor bestowed on scientists by the United States government.

[Return to Table of Contents](#)



Collins' refusal of the half-million dollar prize money is a high-profile testament to his commitment to the highest standards of ethics at NIH. (Photo courtesy of NIH)

Forum to Address Indoor Environmental Exposures

By Laura Hall

NIEHS/NTP Director Linda Birnbaum, Ph.D., will give the keynote address at a community forum on indoor environmental exposures at the Harlem School of the Arts in New York City on April 13. The forum, “[Healthy Homes and You](#),” will include scientific presentations and a panel discussion.

The event, which is open to the public, is sponsored by NIEHS, the [NIEHS Center for Environmental Health in Northern Manhattan \(CEHNM\)](#) and NIEHS grantee [West Harlem Environmental Action, Inc. \(WE ACT\)](#), a non-profit, community-based environmental justice organization.

The goal, explained co-hosts Regina Santella, Ph.D., director of the CEHNM, and Peggy Shepard, executive director of WE ACT, is to use translational research to address community concerns and improve environmental health.

CEHNM is housed at the Columbia University Mailman School of Public Health in New York. The center seeks to improve public health through multidisciplinary scientific approaches and public partnerships with community organizations. CEHNM frequently partners with WE ACT on environmental justice issues.

Scientific Presentations

Beginning at 2:00 pm, Santella will welcome attendees and introduce the speakers. The presenting CEHNM scientists – Matthew Perzanowski, Ph.D., Robin Whyatt, DrP.H., and Patrick Kinney, Sc.D. – will discuss the impact of exposures on public health, including mouse allergens, endocrine disrupting substances, and air pollution. Shepard will discuss translating science to policy in the final presentation of the afternoon session. A discussion with the audience will follow the talks.

Panel Discussion

At 6:00 pm, Shepard will welcome everyone and explain the discussion format. The panelists include Joseph Graziano, Ph.D., of CEHNM, Birnbaum, Ray Werner of the Environmental Protection Agency, Daniel Kass of the New York City Department of Health and Mental Hygiene, Whyatt of CEHNM, and Ray Lopez of the Little Sisters of the Assumption Family Health Service.



“Community forums represent an important means by which NIEHS establishes and maintains a two-way dialog with individuals and communities,” said Dearry. “This ongoing discourse with the public helps to inform the Institute’s planning in many areas, from air pollution to pesticide and heavy metal exposure.” (Photo courtesy of Steve McCaw)



“Informing and empowering the community is the great benefit of these forums,” said Schelp. “People learn about environmental factors that can affect their health and about translating that knowledge into action — to make lifestyle changes and, sometimes, to work for regulatory changes.” (Photo courtesy of John Schelp)

Organizers

- CEHNM — Santella, David Evans, Ph.D., Graziano, and Gail Garbowski
- WE ACT — Shepard, Ogonnaya Dotson-Newman and Anhthu Hoang, Ph.D., J.D., and Cecil Corbin-Mark
- NIEHS — Senior Advisor Allen Dearry, Ph.D., and John Schelp, liaison to the NIEHS Public Interest Partners and a community forum coordinator

(Laura Hall is a biologist in the NIEHS Laboratory of Pharmacology currently on detail as a writer for the Environmental Factor.)

[Return to Table of Contents](#)

Biomedical Career Fair Coming April 30

By Laura Hall

[Registration](#) for NIEHS and Environmental Protection Agency (EPA) postdoctoral fellows began March 19 for the [13th Annual NIEHS Biomedical Career Fair](#) to be held at the EPA conference facility on April 30. Registration for NIEHS and EPA fellows, attendees from elsewhere, and exhibitors is free:

- Postdoctoral fellows from nearby universities can start registering two weeks prior to the event
- NIEHS Trainees Assembly (NTA) invites exhibitors from local companies, organizations, and colleges to [register](#) at any time up to April 17

The career fair is a one-day event where postdoctoral fellows and advanced graduate students can develop job hunting skills in workshops, network with company representatives, and learn about science career opportunities to help in planning their future careers. Members of the NIEHS Trainees Assembly, an organization of non-tenure, non-permanent scientists training at the Institute together with fellows from EPA plan and organize the event with help from NIEHS.

Raj Gosavi, Ph.D., co-chair of the NIEHS Career Fair Committee, and NIEHS Deputy Scientific Director William Schrader, Ph.D., will present welcome and opening remarks. David G. Jensen, founder and managing director of CareerTrax, Inc., will give the keynote address, “Street Savvy Science: Aligning Your Career Goals with Job Market Realities.”



The Career Fair gives trainees a chance to meet and talk with former NIEHS postdocs and young investigators about how they navigated the sometimes choppy waters between training and career. Shown above, left to right, are attendees of the 2008 fair, former postdocs Monty Hughes, Ph.D., and Joel Meyer, Ph.D., with ONES awardee Patricia Opresko, Ph.D. (Photo courtesy of Steve McCaw)

According to past attendees, the career fair can help with finding future jobs and honing job-hunting skills. “I really enjoyed last year’s career fair and found the seminar on writing a resume for a non-academic job very helpful,” said Ashley Godfrey, Ph.D., a postdoctoral fellow in the Laboratory of Molecular Carcinogenesis.

Postdoctoral Fellow Corinne Zeller-Knuth, Ph.D., introduced herself to one of the panelists during the 2007 career fair, which led to her first job teaching at a college. “While I’ve decided that a teaching intensive career isn’t for me and have returned to the NIEHS for postdoctoral training, it was a great experience and the career fair was essential in the process,” said Zeller-Knuth.

(Laura Hall is a biologist in the NIEHS Laboratory of Toxicology and Pharmacology currently on detail as a writer for the Environmental Factor.)

Sessions in Science Career Options at the Career Fair:

- Academic teaching and research
- Regulatory affairs and science policy
- Big pharmaceutical and small biotech industries
- Business entrepreneurship and applied science
- Clinical and translational research
- Science communication and outreach

[Return to Table of Contents](#)



Between sessions, attendees have opportunities to visit vendor displays. (Photo courtesy of Steve McCaw)



Wherever it happens, one of the most important advantages of the NIEHS Biomedical Career Fair is facilitated networking. Duke University Postdoctoral Fellow and Research Associate Ravi Metlapally, Ph.D., left, talked with a representative of the biotech company Athenix during last year’s fair. (Photo courtesy of Steve McCaw)

Science Notebook

Pesticide Exposure and Child Development

By Thaddeus Schug

On March 16, epidemiologist and NIEHS [grantee](#) Brenda Eskenazi, Ph.D., visited NIEHS to discuss her research with farm workers in California, which involves determining how pesticide exposure impacts child development and reproductive health and field testing interventions as primary prevention measures to protect workers and their families from harmful exposures.

[Eskenazi](#), who is the Jennifer and Brian Maxwell Professor of Maternal and Child Health and Epidemiology at the University of California, Berkeley (UCB), presented a Distinguished Lecture seminar titled “Organophosphate Pesticide Exposure and the Development of Children Living in an Agricultural Community: Results of the CHAMACOS Study.” The lecture was hosted by NIEHS Principal Investigator [Matthew Longnecker, M.D., Sc.D.](#)

Eskenazi directs the NIEHS/EPA-funded [CHAMACOS Center](#), named after the word for “small child” in Mexican Spanish (see [text box](#)). The project is a longitudinal birth cohort study that has followed a population of children from before birth through age 9. Data was gathered on 536 infants, born in 2000-2001, whose mothers were enrolled during pregnancy. As Eskenazi explained, “The goal of this ongoing study is to assess the health effects of low-level, chronic pesticide exposure and other exposures in children living in an agricultural community based in the Salinas Valley of California. We also hope to reduce exposures to children by intervention and community outreach programs.”

Pesticide exposure in children living in an agricultural community

The Salinas Valley, considered the “Salad Bowl of the World,” is one of the world’s richest agricultural areas. Eskenazi noted that “take-home” pesticide exposure — on clothing and skin — was extremely



Eskenazi heads the CHAMACOS center, which is investigating the relationship of the environment to children’s health and developing interventions that reduce the incidence of environmentally related childhood disease. (Photo courtesy of Steve McCaw)



Host Matthew Longnecker, right, head of the Biomarker-based Epidemiology Group, shares similar research interests with Eskenazi in regard to pesticide exposures — particularly among pregnant women. (Photo courtesy of Steve McCaw)

high for the workers and their families whose homes, schools, and playgrounds were located very close to cultivated fields. Eskenazi's team measured exposure by analyzing blood, urine, skin, teeth, clothing, soil samples, and data collected from California state agriculture records.

Eskenazi said that pregnant women in the study showed higher organophosphate (OP) urinary metabolite levels than did women of child-bearing age who participated in the National Health and Nutrition Examination Survey (NHANES). Levels in samples collected in the postpartum period were about twice as high as levels during pregnancy. Higher levels of OP pesticide metabolites in maternal urine during pregnancy were associated with shorter gestational duration. A ten-fold increase in average dimethyl, but not diethyl, phosphate metabolites was associated with a decrease of three days in gestational duration.

Lower levels of acetyl cholinesterase — suggesting higher OP exposure — in umbilical cord blood were also associated with significantly shorter length of gestation. No adverse associations were found between OP exposure and infant birth weight, length, or head circumference. However, neonates whose mothers had higher OP pesticide metabolite levels during pregnancy were more likely to have abnormal reflexes in the neonatal period as assessed by the Brazelton Neonatal Behavioral Assessment Scale. OP exposure was associated with both an increase in the number of abnormal reflexes and with the proportion of infants with more than three abnormal reflexes.

PON1 as a Predictor of Pesticide Susceptibility

“Given the same level of pesticide exposure, some individuals may be more susceptible to the potential adverse effects of pesticides depending on their genetic makeup and expression of genes encoding key metabolic enzymes,” Eskenazi observed.

“For example, the human enzyme paraoxonase (PON1) detoxifies various organophosphate pesticides with different efficiency, depending on the main single nucleotide polymorphism (SNP) at position 192 and other SNPs along promoter and coding regions.”



Eskenazi's lecture drew a capacity audience from throughout the Institute to NIEHS Rodbell Auditorium. (Photo courtesy of Steve McCaw)



NTP endocrinologist Sue Fenton, Ph.D., questioned Eskenazi about whether the high rates of obesity in the CHAMACOS study children were related to food insecurity. (Photo courtesy of Steve McCaw)



Shown left to right, NIEHS scientists Yixing (Emily) Zhou, Ph.D. Elizabeth Maull, Ph.D., Kimberly McAllister, Ph.D., Jennifer Collins, Stephanie London, M.D., Dr.P.H., and Les Reinlib, Ph.D., ponder the implications of Eskenazi's findings about pesticide exposure and childhood disease. (Photo courtesy of Steve McCaw)

The pesticide susceptibility project is determining PON1 genotype for two polymorphisms, 192 and 108, and measuring enzyme activity levels — paraoxonase, diazoxonase, chlorpyrifos oxonase, and arylesterase — in maternal and child blood from the CHAMACOS cohort. “We will also examine whether PON1 status modifies the association of pesticides and neurodevelopment,” said Eskanazi.

Center for the Health Assessment of Mothers and Children of Salinas

The CHAMACOS Center works with families in a farm worker community to learn how pesticides and other environmental exposures affect the health of mothers and children. The center is comprised of several research projects investigating the environment and children’s health in the Salinas Valley, Monterey County, Calif.

CHAMACOS is a project of the UCB Center for Children’s Environmental Health Research, in partnership with Natividad Medical Center, Clinica de Salud del Valle de Salinas, and other community organizations. The center has a strong community base, with an Advisory Board and Farm Worker Council, which earned it a Chancellor’s Community-University Partnership Award in 2002.

The goals of the UC Berkeley Children’s Center and CHAMACOS study are:

- To assess pesticide and other environmental exposures in pregnant women and young children;
- To examine the potential health effects of these exposures on childhood growth, neurodevelopment, and respiratory disease;
- To learn more about the mechanisms of pesticide immunotoxicity and neurotoxicity;
- To develop community-based outreach and interventions that reduce take-home pesticide exposure among children of farm workers.

(Thaddeus Schug, Ph.D., is a postdoctoral research fellow in the NIEHS Laboratory of Signal Transduction.)

[Return to Table of Contents](#)

Endocrine Disrupting Compounds and Women’s Health

By Tara Ann Cartwright

NIEHS and NTP took center stage March 2 on the NIH campus with a seminar on “Environmental Exposures and Women’s Health” sponsored by the NIH Office of Research on Women’s Health (ORWH). Broadcast from the NIH Lipsett Amphitheater in Bethesda (watch [video](#)), the event featured four experts whose scientific research explores associations between exposure to environment contaminants, such as endocrine disrupting compounds (EDCs), and increased risk of disease among women.

In her welcoming remarks, NIEHS/NTP Director Linda Birnbaum, Ph.D., underscored the Institute’s mission to foster the critically needed research on environmental contaminants that continue to influence women’s health and wellbeing. Birnbaum also discussed how research at NIEHS has made vital contributions to understanding women’s health and reproductive issues and will continue to pursue solutions to these critical health problems

— work that she said “is near and dear to my heart as a woman, a scientist, and the first female director [of NIEHS].”

NTP reproductive endocrinologist Suzanne Fenton, Ph.D.

Fenton opened the seminar with a talk exploring “Early Life Environmental Exposures: Lifelong Impact of Mammary Gland Development and Function.” Fenton, a group leader in the Cellular and Molecular Pathology Branch at NIEHS, utilizes rodent models to examine the effects of prenatal and lactational EDC exposure on mammary gland development.

Fenton demonstrated that exposure to the three EDCs, dioxin, atrazine, and perfluorooctanoic acid (PFOA) induced abnormal development of the mammary gland, including decreased ductal branching and delays in the differentiation of terminal buds. Fenton’s animal studies of early life exposure effects on sexual development and the impact on other aspects of health set the stage for the speakers who followed her.

NICHD Postdoctoral Fellow Maureen Cooney, Ph.D.

Moving from basic research to epidemiology, the second speaker in the seminar lectured on “Environmental Influences on Female Fecundity and Fertility.” Cooney, a postdoctoral fellow in the Epidemiology Branch at The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) directed by Germaine Buck Louis, Ph.D., focused primarily on the interplay between EDCs and female reproduction and development.

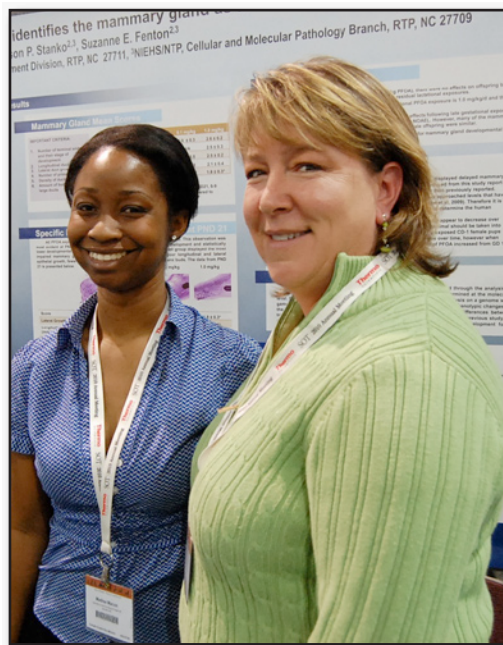
According to Cooney, NICHD is presently conducting two research efforts addressing reproductive health end points, the LIFE (Longitudinal Investigation of Fertility in the Environment) and ENDO (Endometriosis: Natural History, Diagnosis, and Outcomes) studies. The LIFE study assesses the reproductive and developmental toxicity of environmental chemicals among couples at risk for pregnancy, while the ENDO study examines the relationship between environmental chemicals and endometriosis.

NIEHS grantee Brenda Eskenazi, Ph.D.

Following Cooney was grantee Brenda Eskenazi, a professor of maternal and child health and epidemiology in the School of Public Health at the University of California at Berkeley. Eskenazi’s lecture explored “Early Exposure to Endocrine Disruptors and its Effects on Women’s Health: Evidence from Two Longitudinal Studies.” Eskenazi is the principal investigator of the Seveso Women’s Health Study, which found that young children who were exposed to dioxin during the Seveso, Italy disaster — an explosion in 1976 that exposed the surrounding population to some of the highest levels recorded in humans — have an increased risk in developing early menarche. This study is currently examining the relationship of dioxin to breast cancer, diabetes, obesity, and metabolic syndrome.



Birnbaum filmed her message beforehand because she was unable to attend and show her support in person. Her remarks followed an introduction by ORWH Director Vivian Pinn, M.D. (Photo courtesy of Steve McCaw)



Fenton, shown above at SOT with a coauthor, University of North Carolina toxicology student Madisa Macon, was lead speaker at the event. The seminar highlighted a series of investigators whose common research goal is to increase the understanding of how the environment influences women’s diseases and disorders. (Photo courtesy of Ed Kang)

Eskenazi also discussed her work at the Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS), which she covered in more depth during a Distinguished Lecture Seminar Series talk at NIEHS later in the month (see related [story](#)).

NIEHS grantee Jose Russo, M.D.

Concluding the event was [Jose Russo](#), director of both the Fox Chase Breast Cancer Research Laboratory (BCRL) and the NIEHS-National Cancer Institute Breast Cancer and the Environment Research Centers (BCERC) at the Fox Chase Cancer Center. Russo spoke on how prepubertal and prenatal exposure to bisphenol A (BPA) increases the tumorigenic response in the mammary gland. Russo's current studies have demonstrated that prenatal exposure of BPA induced phenotypic changes in mammary tissue and genotypic changes in resulting tumors. He said these tumors had an earlier onset and were larger in diameter, more aggressive, abundant, and more undifferentiated.

Russo pursues his research through [NIEHS Breast Cancer Center](#) and [research](#) grants.

(Tara Ann Cartwright, Ph.D., is a postdoctoral fellow in the NIEHS Laboratory of Neurobiology Membrane Signaling Group.)

[Return to Table of Contents](#)

Postdoc Brings Home SOT Awards

By Eddy Ball

NIEHS research fellow Xueqian (Shirley) Wang, Ph.D., received first-place prizes for her poster at the annual Society of Toxicology (SOT) meeting, March 7–11 in Salt Lake City. [Wang](#) has been part of the NIEHS Laboratory of Toxicology and Pharmacology Intracellular Regulation Group, headed by Principal Investigator and Chief [David Miller, Ph.D.](#), for the past three years.

Wang was doubly fortunate with special interest group (SIG) and specialty section (SS) awards for her poster, "The Aryl Hydrocarbon Receptor Regulates ABC [ATP-binding cassette] Transporters at the Blood-Brain Barrier." Her first honor came early in the meeting with the [American Association of Chinese in Toxicology \(AACT\)](#) SOT-SIG and Charles River Best Abstract Award of a plaque and \$300. On March 10, Wang learned she had also won the first-prize [Neurotoxicology SS Postdoctoral Fellow Poster Award](#).

In her submission letter, Wang said, "Given the role of ABC transporters in drug pharmacokinetics, our research has important



Representing the NIEHS Office of the Director at the event was Legislative Liaison Mary Gant, above, who introduced the speakers. (Photo courtesy of Steve McCaw)



Wang said of her awards, "It was a great honor to me and our laboratory that my poster won the NTSS first-place award and AACT Best Abstract Award. I could not have accomplished this without the great research environment at NIEHS." (Photo courtesy of Steve McCaw)

implications, especially with regard to the interactions between environmental contaminants and pharmacotherapy for both the CNS (central nervous system) and the periphery.”

Citation: Wang X, Hawkins BH, Sykes D, Miller SD.
[The Aryl Hydrocarbon Receptor \(AhR\) Regulates P-glycoprotein at the Blood-Brain Barrier \(BBB\).](#)
Laboratory of Pharmacology, NIH/NIEHS

[Return to Table of Contents](#)



Wang, left, demonstrated her team spirit last July as she and Miller, right, kicked off the “I Am Intramural” campaign at NIEHS (see [story](#)). (Photo courtesy of Steve McCaw)

Yale Postdoc Honored for Best Publication

By Eddy Ball

A Yale postdoctoral fellow supported by NIEHS was one of three young scientists honored for Best Postdoctoral Publications at the annual meeting of the Society of Toxicology (SOT) in Salt Lake City March 7–11. SOT recognized Bret Bessac, Ph.D., first author on the 2009 The Federation of American Societies for Experimental Biology’s FASEB Journal [paper](#) “Transient Receptor Potential Ankyrin 1 Antagonists Block the Noxious Effects of Toxic Industrial Isocyanates and Tear Gases.”

Bessac is one of what is known around the Yale Department of Pharmacology as a [Jordtian](#) — a member of the lab headed by NIEHS Outstanding New Environmental Scientist (ONES) [awardee](#) Sven-Eric Jordt, Ph.D.(see [story](#)), who is also the principal investigator on a [grant](#) through the [NIH CounterACT Program](#). Bessac’s award-winning paper received support from both of the grants.

Bessac was first author on two other papers supported by Jordt’s ONES and CounterAct funding. In 2008, he and his coauthors published “[TRPA1 Is a Major Oxidant Sensor in Murine Airway Sensory Neurons](#)” in the Journal of Clinical Investigation and “[Breathtaking TRP Channels: TRPA1 and TRPV1 in Airway Chemosensation and Reflex Control](#)” in Physiology. He was also an author on the Jordt group’s ground-breaking 2009 paper, “[A Sensory Neuronal Ion Channel Essential for Airway Inflammation and Hyperreactivity in Asthma](#),” published in the Proceedings of the National Academy of Sciences USA.

Jordt’s grants are administered by NIEHS Health Science Administrators Annette Kirshner, Ph.D., and Elizabeth Maull, Ph.D.

[Return to Table of Contents](#)



Bret Bessac is a part of a national research effort to discover clinical applications for counteracting the effects of noxious agents released in industrial accidents, terrorist attacks, and chemical warfare. (Photo courtesy of Ed Kang)



In 2007, Jordt, shown during a visit to NIEHS in February 2009 (see [story](#)), became the first NIEHS grantee honored with one of the Presidential Early Career Awards for Scientists and Engineers (see [story](#)). (Photo courtesy of Steve McCaw)

Study Confirms Link to Lower Risk of Parkinson's

By Eddy Ball

Long-time smokers may suffer more preventable health problems than non-smokers, but their habit may also dramatically lower their risk of developing Parkinson's disease (PD), according to a new study led by NIEHS epidemiologist [Honglei Chen, M.D., Ph.D.](#)

Like other scientists who have studied the association of smoking with reduced risk for PD, authors of the study pointed out that the adverse health effects of smoking far outweigh any benefits of reduced risk for PD. Understanding the association is important, they maintain, "for determining the clinical usefulness of administering the active constituents of tobacco to new patients with PD and for guiding animal experimental research" into the underlying chemicals and biological mechanisms involved.

The [study](#), which appeared online March 10 in the journal *Neurology*, looked at detailed aspects of smoking over life in relation to PD in more than 300,000 participants of the NIH-AARP (American Association of Retired Persons) Diet and Health (DH) Study. This is the largest single study ever examined in this way, giving the study an unprecedented level of power to its support for the hypothesis that smoking may decrease PD risk.

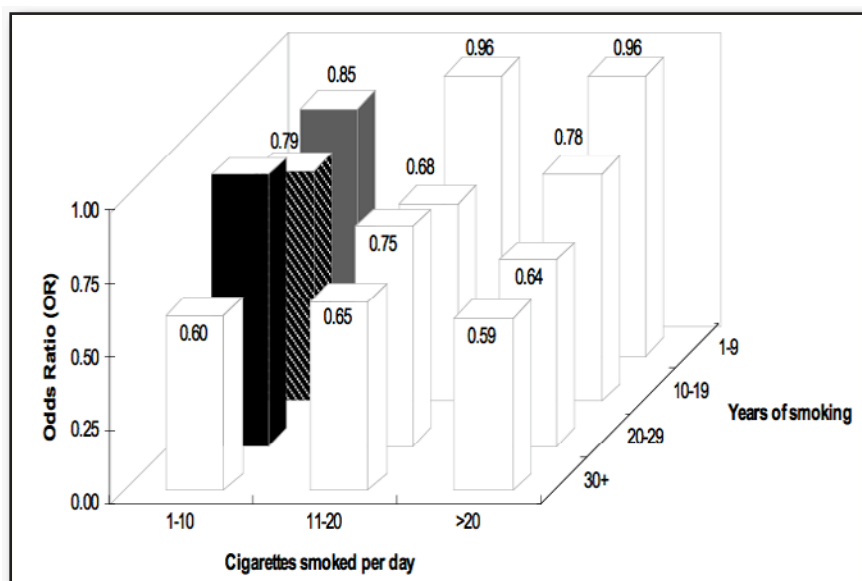
The research team found that long-term and recent smoking were more important than intensity in conferring the protective effects of smoking. "The number of cigarettes smoked per day became irrelevant once adjusted for smoking duration or years since last smoking," the authors observed.

Compared to the reference group of never-smokers in the cohort, people who smoked for 30 years or longer had up to a 41 percent reduction in risk for PD. Participants who reported smoking for fewer than ten years showed a 4 to 15 percent reduction in risk.

The participants were among the more than 550,000 people 50-71 years old enrolled by the NIH-AARP DH study in 1995. They were followed up between 2004 and 2006 with a survey to update lifestyle exposure and occurrence of major chronic disease, including PD. In 2007, the research team began collecting saliva samples from surviving patients with PD for genetic research and validating PD diagnosis in the cohort in attempt to partially offset the limitations of self-reporting.



"Nobody would advocate smoking to prevent Parkinson's disease," said lead author Chen. "It's important to make that very, very clear."
(Photo courtesy of Steve McCaw)



This bar graph from the study shows the dramatic decrease in risk for PD associated with years of smoking. (Graph courtesy of Honglei Chen)

The study was supported by funding from NIEHS and the National Cancer Institute (NCI). In addition to Chen, the interdisciplinary team included NIEHS epidemiologists [Freya Kamel, Ph.D.](#), and [Qun Xu, Ph.D.](#), along with NIEHS biostatistician [David Umbach, Ph.D.](#) Also on the team were researchers from NCI, Pennsylvania State University, and Westat Inc.

Citation: [Chen H, Huang X, Guo X, Mailman RB, Park Y, Kamel F, et al.](#) 2010. Smoking duration, intensity, and risk of Parkinson disease. *Neurology*. Mar 10. [Epub ahead of print]

[Return to Table of Contents](#)

Are We Closer to Effective Treatment for AD?

By *Laura Hall*

NIEHS Principal Investigator [David Miller, Ph.D.](#), and two of his former NIEHS postdoctoral fellows now at the University of Minnesota (UMN) have demonstrated a treatment for mice with Alzheimer's Disease (AD) that reduces AD pathology. The same strategy could be effective in delaying onset and slowing the progression of AD in humans.

In the [study](#), which was partially funded by NIEHS, the researchers established a protein called P-glycoprotein (P-gp) as one of the critical proteins involved in reducing amyloid beta (A β) accumulation in the brain. A β is the neurotoxic protein associated with AD that destroys brain nerve cells, or neurons. In their therapeutic strategy, the scientists targeted pregnane X receptor (PXR), a regulator of P-gp, increasing P-gp levels in brain blood vessels, which in turn decreased brain A β levels.

"Our experiments were done in young AD mice that do not yet have any cognitive impairment — technically, they are considered healthy," said first author [Anika Hartz, Ph.D.](#), research associate in the Medical School at UMN and a former member of Miller's group. "However, we found that their blood-brain barrier (BBB) biochemistry is already significantly changed."

AD causes neurons in the brain to die, resulting in progressive memory loss and the increasing inability to carry out daily functions. It is the most common form of dementia in older people, currently affecting up to 4.5 million people in the U.S. As the U.S. population ages, more people will be affected because the risk of AD doubles for every five-year age interval beyond age 65.

The Treatment

To see whether they could restore P-gp levels in the genetically engineered AD mice, known as hAPP mice (see [text box](#)), the scientists used PXR activation. PXR, a nuclear receptor, senses xenobiotic compounds, binds to these compounds called ligands, and then binds to DNA and controls the expression of drug metabolizing enzymes and certain transporters like P-gp. Upregulating these genes can help to eliminate foreign compounds from the body.



"We are currently preparing for a long-term feeding study, where hAPP mice receive a PXR activating compound through their diet," said first author Hartz. "We will then look at their brains to see if long-term upregulation prevents onset and progression of AD."
(Photo courtesy of Anika Hartz)

Treating the 12-week-old AD mice once a day for seven days with a PXR ligand increased P-gp amounts in brain capillary membranes and P-gp activity levels in capillaries to levels of those in normal control mice. Importantly, brain human A β accumulation in these treated hAPP mice was acutely reduced by up to 60 percent.

The authors said that P-gp transport of A β “may well be the limiting factor in A β brain clearance and one critical step that is defective in AD” and that lowered P-gp expression at the BBB is an “early biochemical manifestation of AD pathology that occurs before cognitive symptoms are evident.” They added that increasing P-gp levels in the BBB during the early stages of AD by targeting signals that upregulate P-gp expression, like PXR, could be a new therapeutic strategy for AD.

Citation: [Hartz AMS, Miller DS, Bauer B. 2010. Restoring blood-brain barrier P-glycoprotein reduces brain A{beta} in a mouse model of Alzheimer’s disease. Mol Pharmacol. February 26, Doi:10.1124/mol.109.061754 \[Epub ahead of print\]](#)

This research was supported in part by the National Institute of Environmental Health Sciences Intramural Research Program [Z01 ES080048].

(Laura Hall is a biologist in the NIEHS Laboratory of Toxicology and Pharmacology currently on detail as a writer for the Environmental Factor.)

[Return to Table of Contents](#)

Protein Transport and the Blood-Brain Barrier

The blood-brain barrier (BBB) separates the body’s circulating blood from the fluid that bathes the brain’s cells. The BBB protects the brain by limiting its exposure to substances in the blood. The major constituent of the BBB is the network of small blood vessels called capillaries that supply the brain cells with nutrients. The capillary walls are lined with endothelial cells.

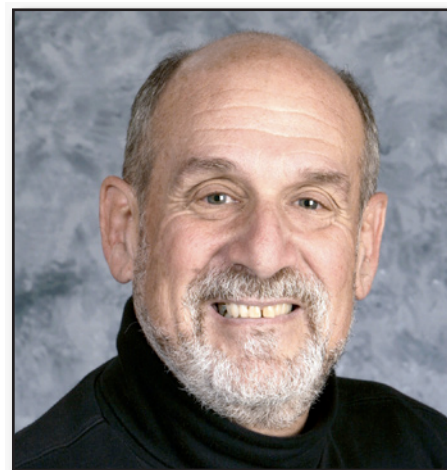
P-gp Transports hA β

Hartz and her colleagues isolated functioning brain capillaries — which closely mimic the BBB *in vivo* — from control mice and AD mice and performed experiments treating the capillaries themselves or the animals before the capillaries were removed. The AD model mice were transgenic, having a human gene that caused overexpression of the human amyloid precursor protein (hAPP). Enzymes cut hAPP *in vivo* to form human A β (hA β).

The scientists showed that P-gp transported hA β across the capillaries into the blood-space — the inside of the blood capillaries — that is, away from the brain. In untreated 12-week-old hAPP mice — which exhibit hA β accumulation in the brain but show no sign of cognitive impairment — brain capillary P-gp protein level and activity was reduced by 70 percent compared to control mice. Other proteins known to move A β into the capillary cells did not contribute to this difference in hA β transport.



“Besides the current \$100 billion health care cost factor, AD is a devastating disease,” said co-author [Bjoern Bauer, Ph.D.](#), assistant professor at UMN. (Photo courtesy of Bjoern Bauer)



“Our paper shows how a basic understanding of three aspects of blood-brain barrier biology — transport protein function, its alteration in neurodegenerative disease, and mechanisms of transporter regulation — provides a new strategy to slow disease progression,” said Miller. (Photo courtesy of Steve McCaw)

Research Offers New Insight into DNA Synthesis

By Bono Sen

A new NIEHS-funded study challenges current thinking about ribonucleotide incorporation into DNA by yeast DNA polymerases and may offer new insights into mechanisms by which the human genome is stabilized and, conversely, may be destabilized. Published online in the Proceedings of the National Academies of Sciences, the study was led by NIEHS Principal Investigator [Thomas Kunkel, Ph.D.](#), and first authored by a former postdoctoral fellow in his group, Stephanie Nick McElhinny, Ph.D.

The [study](#) suggests that ribonucleoside triphosphates (rNTPs) are incorporated into DNA as ribonucleoside monophosphates, or rNMPs, in much higher amounts than may have previously been appreciated. One likely reason for this is that the concentrations of the rNTPs needed for a wide variety of functions in yeast and mammalian cells greatly exceed those of the deoxyribonucleotides (dNTPs) needed for DNA replication and repair.

Most DNA polymerases are thought to efficiently prevent incorporation of rNTPs during DNA synthesis. To test this idea with polymerases that replicate the nuclear genome, these researchers determined the selectivity with which yeast DNA polymerases alpha (Pol α) delta (Pol δ) and epsilon (Pol ϵ) incorporate the monophosphates dNMPs and rNMPs during DNA synthesis *in vitro*. They found that, while all three polymerases prefer to incorporate dNMPs, rNMP incorporation into during DNA was surprisingly high.

Kunkel and his colleagues further showed that rNMP incorporation along a DNA template varied widely as a function of the polymerase, the identity of the base and the sequence context. Based on the estimated amount of DNA copied by the three polymerases during replication *in vivo*, the authors estimated that more than 13,000 rNMPs could be incorporated into DNA during each replication cycle in yeast.

The human genome is 500 times larger, so if human polymerases behave similarly — something that is currently unknown — it is possible that several million rNMPs could be introduced into the human genome during each cell division, potentially making rNMPs the most common of all noncanonical nucleotides introduced into the human genome.

The authors went on to consider the implications of abundant rNTP incorporation into DNA. They considered how rNMPs in DNA might be repaired, as well as the possibility that rNMPs in DNA might be tolerated reasonably well. However, given that ribonucleotides in DNA promote changes in helix geometry, unrepaired rNMPs in DNA may not be totally harmless, for example potentially resulting in mutations.



During her fellowship at NIEHS, Nick McElhinny was a member of the DNA Replication Fidelity Group. (Photo courtesy of Steve McCaw)



Kunkel is head of the Laboratory of Molecular Genetics DNA Replication Fidelity Group, chief of the Laboratory of Structural Biology, and director of the Environmental Biology Program at NIEHS. (Photo courtesy of Steve McCaw)

The researchers also considered the possibility that rNMPs in DNA might have beneficial consequences. They speculated that the presence of helix distorting rNMPs in DNA may serve signaling functions, perhaps for mismatch repair, nucleosome loading, chromatin remodeling, and gene silencing.

Coauthors on the study included scientists from the NIEHS Laboratory of Molecular Genetics, Umeå University in Sweden, and Washington University in St. Louis.

Citation: Nick McElhinny SA, Watts BE, Kumar D, Watt DL, Lundström EB, Burgers PM, Johansson E, Chabes A, Kunkel TA. 2010. Abundant ribonucleotide incorporation into DNA by yeast replicative polymerases. *Proc Natl Acad Sci U S A* Mar 1. [Epub ahead of print]

(Bono Sen, Ph.D., is the science education and outreach program manager for the NIEHS journal *Environmental Health Perspectives*.)

[Return to Table of Contents](#)

Regulation and Mutations of Drug Metabolizing Enzymes

By Laura Hall

On February 25, [Joyce Goldstein, Ph.D.](#), principal investigator of the NIEHS Human Metabolism Group discussed the factors that regulate the gene expression of a superfamily of drug metabolizing enzymes called the human cytochrome P450 enzymes (CYPs) and the effects of mutations or genetic polymorphisms in the *CYP* genes.

In her talk, Goldstein focused on the CYP2C subfamily — CYP2C8, CYP2C9, CYP2C18, and CYP2C19 — which metabolize approximately 25 percent of all clinically prescribed drugs. Understanding *CYP2C* gene regulation provides insight into drug-drug interactions and drug tolerance.

Goldstein's [Laboratory of Toxicology and Pharmacology \(LTP\)](#) Seminar Series presentation, titled "The Human Cytochrome P450 2C(CYP2C) Xenobiotic Metabolizing Enzymes: Their Medicinal Importance, Genetic Polymorphisms, and Transcriptional Regulation" was hosted by David Miller, Ph.D., chief of the LTP.

The Goldstein laboratory first cloned and identified two members of the human CYP2C subfamily enzymes in 1991 and expressed all four members of this subfamily in yeast — identifying drug substrates for all four human enzymes. Goldstein's studies first established the human genomic sequences for this subfamily and her collaborations with clinical researchers have helped to identify human genetic polymorphisms in the *CYP2C* genes and to test their clinical consequences.



"Those individuals who have two null alleles in the CYP2C19 gene and take Plavix might as well be taking starch pills," said Joyce Goldstein (above). "The mutated CYP2C19 enzyme cannot metabolize the drug into its active form. Individuals with mutated genes are common, particularly among Asian populations." (Photo courtesy of Steve McCaw)

CYP2C Gene Polymorphisms

CYP2C9 metabolizes warfarin, the anticoagulant drug prescribed to reduce the chance of blood clots that can cause heart attacks and strokes. Goldstein explained that two predominant mutant variants of the *CYP2C9* gene affect the ability of the enzyme products to function properly. Individuals with one or two of any combination of these variants metabolize warfarin poorly, so that normal, “safe” doses can be toxic.

The lower the amount of warfarin metabolized, the greater the concentration of drug that can accumulate in the body — possibly resulting in overdosage — and polymorphisms have been shown to produce serious and life-threatening bleeding problems.

Research characterizing the function of and identifying the human mutations in the *CYP2C9* gene has led to warnings on warfarin packaging inserts. The warning makes doctors aware that patients with these mutated genes require lower doses.

Mutations in the *CYP2C19* gene discovered by the Goldstein laboratory affect the metabolism of the anti-clotting drug Plavix and have been shown to be associated with a 50 percent increase in death and a 5-fold increase in stent failures in patients with cardiovascular disease treated with Plavix, which now bears a **boxed warning** about the drug’s ineffectiveness in some patients with a genetic mutation.

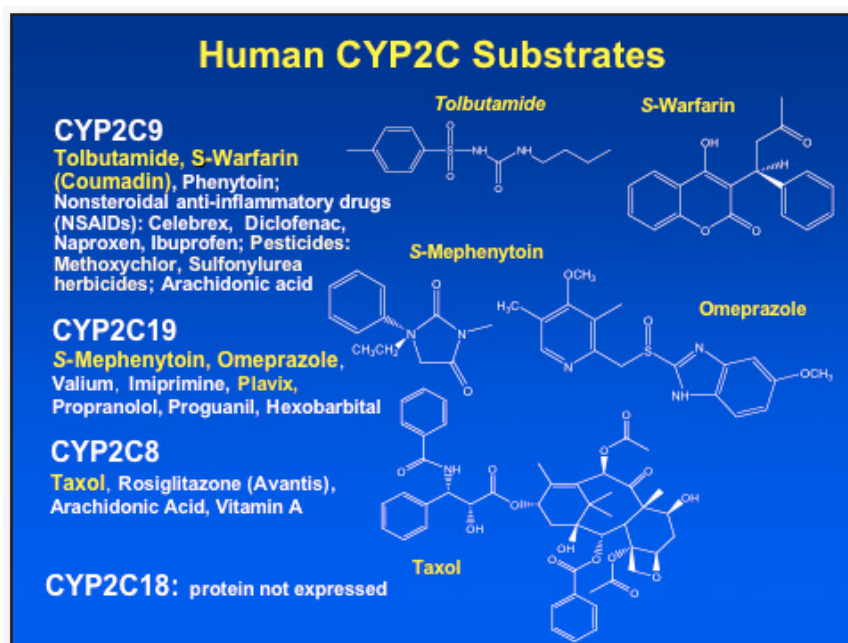
CYP2C Gene Regulation

Variability in CYP2C enzyme expression can also make a difference in how much drug can be metabolized. To understand how *CYP2C* gene expression can be altered, Goldstein is investigating the role of nuclear receptors — constitutive androstane receptor (CAR), pregnane X receptor (PXR), and the important liver enriched hepatocyte nuclear factor four alpha (HNF4α) — in regulating *CYP2C* gene transcription.

CAR and PXR are cellular proteins that sense exogenous chemicals and activate expression of the CYP2C and other detoxification enzymes to help eliminate these foreign chemicals from the body.

Goldstein’s group has identified HNF4α binding sites and a CAR/PXR binding site in the promoter regions of the *CYP2C* genes. Promoter regions of a gene are not protein product template, but help initiate transcription or copying of DNA into the RNA that will be used to make protein.

In the liver, *CYP2C* genes are constantly expressed at a basal level, but they can be upregulated by exposure to chemicals. Goldstein’s group has demonstrated that the HNF4α sites are involved in the basal expression, whereas both CAR/PXR and HNF4α sites are needed for optimal induction of *CYP2C9* and *CYP2C8* gene transcription.



CYP2C enzymes metabolize many drugs. Common mutations in the *CYP2C19* gene are associated with increased adverse effects of Plavix in patients. Genetic tests for these mutations are covered by an NIEHS patent and are being considered for individualized medicine for *CYP2C19* substrates, said Goldstein. (Slide courtesy of Joyce Goldstein)

The scientists determined that CAR and PXR were not directly bound to the HNF4 α site. A coactivator, nuclear receptor coactivator 6 (NCOA6), appears to form a bridge between one HNF4 α and the CAR/PXR site. A second coactivator, mediator complex subunit 25 (MED25), binds to HNF4 α and helps recruit the transcription enzyme RNA polymerase II to a mediator complex needed to initiate gene transcription.

(Laura Hall is a biologist in the NIEHS Laboratory of Toxicology and Pharmacology currently on detail as a writer for the Environmental Factor.)

[Return to Table of Contents](#)

Benefits of Stem Cell Research

By Laura Hall

On March 18, [Guang Hu, Ph.D.](#), principal investigator of the Stem Cell Biology Group discussed how studying embryonic stem cells can lead to a greater understanding of embryonic development and disease mechanisms and lead to advances in gene therapy. The Laboratory of Molecular Carcinogenesis (LMC) Seminar Series talk, titled “RNAi Screen Identified Novel Players in Embryonic Stem Cell Self-Renewal,” was hosted by Thomas Eling, Ph.D., of the Eicosanoid Biochemistry Group.

In his introduction, [LMC Chief Trevor Archer, Ph.D.](#), told the capacity audience that Hu would “describe a new group of genes that are important for the process of stem cell renewal and pluripotency.”

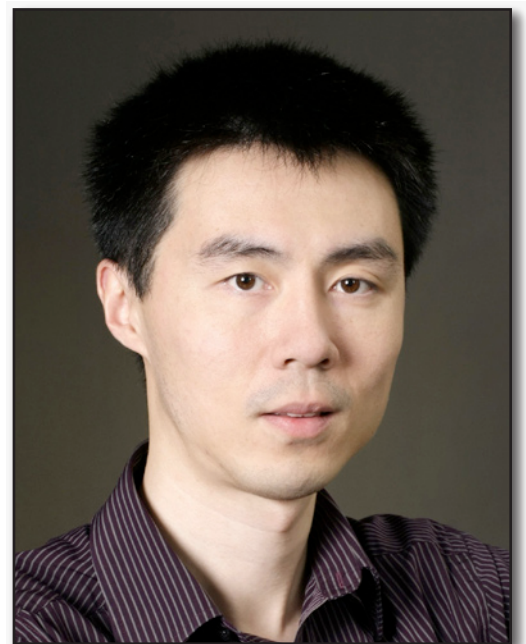
Tapping the potential of differentiation

Embryonic stem cells (ESCs) are derived from the inner cell mass of a very early developmental embryo stage. Unlike most cells, an ESC can change or differentiate into any type of cell — an ability called pluripotency. ESCs can also divide indefinitely without differentiating, giving them the capability of self-renewal. How ESCs are able to differentiate and self-renew is not well understood.

However, as Hu explained, understanding the molecular basis of ESC differentiation and self-renewal processes has great benefits. ESC differentiation serves as a good model to study the complex events that occur during embryonic development in mammals.

Knowledge gained from stem cell research can help to further regenerative medicine. Human induced pluripotent stem cells (iPSCs) are formerly differentiated somatic, or “normal,” non-stem cells that have been induced or reprogrammed into an ESC-like state. Like ESCs, iPSCs can be induced to differentiate into a desired cell type allowing for the correction of genetic mutations that cause disease in patients.

In gene therapy, the corrected cells would be transplanted back into the patient to alleviate symptoms and hopefully prevent the expression of the disease. The iPSCs are a nearly identical match to the cell donor and would be unlikely to cause immune rejection problems — giving them great potential for regeneration of damaged tissue.



“The ultimate goal is to use functional genetic approaches to identify genes and pathways in the self-renewal and differentiation of stem cells,” said Hu. “We hope to discover a more complete view of these processes to understand developmental biology better and also to contribute to the development of regenerative medicine.” (Photo courtesy of Steve McCaw)

Studying ESCs can shed light on the derivation of iPSCs and the desired cell types for cell-based therapies. Also, for many diseases, such as amyotrophic lateral sclerosis, there are no cell culture models to study. This lack hinders research trying to identify possible disease mechanisms or drug targets. Deriving the cell types affected by the disease from stem cells “opens up a new window to investigate what is the cause, what is behind the symptoms,” said Hu. Specific cells can also be derived and used for drug screening to find new drugs to treat disease effectively.

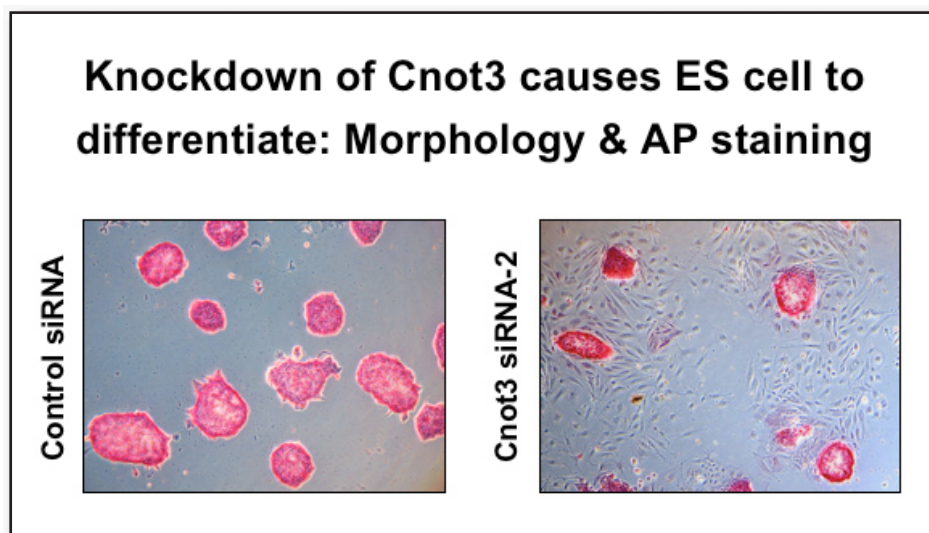
Self-renewal genes

Hu and colleagues have screened the genome of mouse ESCs to identify genes that are needed to maintain self-renewal. In his talk he focused on two of the genes, CCR4-Not transcription complex subunit 1 (Cnot1) and subunit 3 (Cnot3). The Cnot complex regulates transcription, but different components of the complex appear to have different functions, and only Cnot1 and Cnot3 showed up as self-renewal genes.

When Hu knocked down the Cnot1 or Cnot3 genes in his mouse ESCs, he found that numerous differentiation marker genes were upregulated and the cells changed their morphology, or appearance, to look more like differentiated cells. However, the selected cells did not differentiate into specific cell type lineages, suggesting that the two Cnot genes were probably more involved in maintaining self-renewal rather than causing differentiation.

Hu plans to further test Cnot1 and Cnot3 by creating conditional knockout mice to see if these genes are important in embryonic development. Other studies in ESCs will identify the downstream targets of the two genes and the composition of the Cnot complex, and determine if Cnot1 and Cnot3 impact the initiation of pluripotency when adult cells are induced to become iPSCs.

Hu will also validate and study other genes identified in his screen to try to understand the molecular basis of self-renewal in ESCs.



In culture, embryonic stem cells form compact cell cluster colonies and show red alkaline phosphatase staining — a marker for stem cells. Silencing the Cnot3 gene results in cells that begin to show differentiated cell structure and loss of staining. (Photos courtesy of Genes and Development)

(Laura Hall is a biologist in the NIEHS Laboratory of Toxicology and Pharmacology currently on detail as a writer for the Environmental Factor.)

[Return to Table of Contents](#)

This Month in EHP

By Eddy Ball

French fries on the cover of the April 2010 [Environmental Health Perspectives \(EHP\)](#) could make mouths water — at least until readers digest the story behind the photo. “A Matter of Degrees: Advancing Our Understanding of Acrylamide” reports on the ways high-temperature cooking processes — frying, grilling, and roasting — produce chemicals, such as acrylamide and advanced glycation end products, that can adversely affect health.

Also making the news section this month is the article “Mystery in a Bottle” that ponders whether the U.S. Environmental Protection Agency will require public disclosure of pesticide inerts — ingredients in products serving any purpose besides actually deterring the pest at hand. Under current policy, manufacturers are not required to disclose these ingredients. Critics point out that these inerts are not necessarily harmless and that some actually pose threats to health.

Along with a review of “Air Pollution and Asthma in Children,” featured studies in this issue include:

- “POPs [Persistent Organic Pollutants] and Insulin Resistance Syndrome”
- “ToxCast: Prioritization of Chemicals for *In Vitro* Screening”
- “Atrazine Alters Frog Development in Natural Pond Settings”
- “Prenatal Phthalate Exposure and Childhood Behavior”
- “Flame Retardants and Human Brain Cells”

[Return to Table of Contents](#)



<http://twitter.com/ehponline>



Upcoming Distinguished Lecturer Stephen West

By Eddy Ball

The NIEHS Distinguished Lecture Series highlights the links between mutagenesis and cancer with a talk on April 13 by Stephen West, Ph.D. Hosted by Laboratory of Molecular Genetics Staff Scientist [Dmitry Gordenin, Ph.D.](#), West’s lecture will explore “Defective DNA Strand Break Repair and Links to Inheritable Disease.”

[West](#) is currently the associate director of Clare Hall Laboratories, a division of the Cancer Research United Kingdom London Research Institute (LRI), and senior group leader of the Genetic Recombination Laboratory there. In 1995, West was elected a fellow of the Royal Society. He has also received several other prestigious awards for his work, including the Swiss Bridge Prize Award for Cancer Research in 2001 and again in 2009, the Louis-Jeantet Prize for Medicine in 2007, and the Novartis medal and prize from the Biochemical Society in 2008.

The [West Group](#) specializes in basic research into mechanisms of DNA replication, recombination, repair, and cell cycle, exploring the relationships between genome instability and cancer. The group is recognized for its research into the genome instability associated with mutations in the BRCA genes, which is caused by defective recombination processes and appears to underlie certain inheritable breast and ovarian cancers. According to West, approximately 20 percent of breast cancers are inheritable, and of those about one-third have been linked to mutations in BRCA1 or BRCA2.

West has also made important discoveries about loss of activity of the protein Aprataxin, which plays a critically important cellular role in guarding the genome against DNA damages that would otherwise pose a block to normal cellular processes. His group defined this molecular defect and its role in the neurological disorder known as Ataxia with Oculomotor Apraxia-1 (AOA1).

In 2008, the West Group identified a key enzyme in mammals, ResA, which is involved in the process of homologous recombination — one of the ways an organism repairs breaks in its DNA. A defect in the production of this specialized enzyme, one of what are called the Holliday junction resolvases, short-circuits the proper chromosome segregation necessary for DNA repair.

[Return to Table of Contents](#)



After completing a postdoctoral fellowship and serving as a research scientist in the Department of Therapeutic Radiology at Yale University, West returned to his native England in 1989. (Photo courtesy of Stephen West)

Extramural Papers of the Month

By Jerry Phelps

- [Aging Protein Function Revealed](#)
- [Living Near a Major Roadway Linked with Atherosclerosis](#)
- [Blood Type and Pancreatic Cancer Linked](#)
- [African Ancestry and Asthma](#)



Read the current Superfund Research Program [Research Brief](#). New issues are published on the first Wednesday of each month.

Aging Protein Function Revealed

An NIEHS-funded research team has discovered that the protein sestrin plays a key role in regulating aging and metabolism.

The work was carried out in fruit flies bred with an inactivated sestrin gene. The fruit flies began showing signs of premature aging at 20 days of age, which is roughly equivalent to 20 years in humans. The flies began accumulating high levels of triglycerides, showed signs of muscle degeneration, and had a high percentage of defective mitochondria in their muscle cells. Much of this damage was prevented by providing vitamin E as a source of antioxidants, replacing one of the natural functions of sestrin.

Sestrin is known to inhibit an enzyme called TOR, or target of rapamycin, an immunosuppressant drug used in organ transplant patients that has been shown to extend the lifespan of healthy mice up to 14 percent. However, the effects of the long-term use of rapamycin are not well known. The team also found that sestrin activates another protein called AMPK that is also activated by caloric restriction, which has been shown to increase the life span of several animals.

Mammals have three types of sestrin proteins, all very similar. The team plans additional research with mice aimed at determining whether sestrins or molecules that activate sestrin production could be useful in preventing or treating mitochondrial dysfunctions that lead to a number of chronic diseases and dysfunctions.

Citation: [Lee JH, Budanov AV, Park EJ, Birse R, Kim TE, Perkins GA, et al.](#) 2010. Sestrin as a feedback inhibitor of TOR that prevents age-related pathologies. *Science* 327(5970):1223-8.

[Return to Table of Contents](#)

Living Near a Major Roadway Linked with Atherosclerosis

NIEHS grantees presented the first epidemiologic evidence supporting the idea of a chronic vascular response to exposure to particulate matter air pollution. They found that the progression of atherosclerosis was more than twice as fast for people living within 100 meters of a major highway in Southern California.

The team used data from five Los Angeles-based double-blind randomized clinical trials that assessed effects of various treatments on the change in carotid artery intima-media thickness (CIMT), a marker for sub-clinical atherosclerosis. They used models to estimate the home outdoor concentrations of particulate matter air pollution and classified the subjects' homes by proximity to traffic-related pollution. Particulate matter pollutions levels and traffic proximity were positively associated with CIMT progression.

The researchers warn that it may be premature to conclude that particulate matter pollution and its constituents are the sole cause of the progression of the arterial thickening. Atherosclerosis results from complex processes that may include a combination of various urban pollutants, host factors, and pathways that ultimately lead to the association.

Given the leading role of heart disease as a cause of death in most westernized countries and the growing contribution in developing countries, these findings may be of high public health relevance. Further investigations need to focus on susceptible groups and follow-up of cohorts to investigate the effect of air pollution on the progression of CIMT.

Citation: [Künzli N, Jerrett M, Garcia-Esteban R, Basagaña X, Beckermann B, Gilliland F, et al.](#) 2010. Ambient air pollution and the progression of atherosclerosis in adults. *PLoS One* 5(2):e9096.

[Return to Table of Contents](#)

Blood Type and Pancreatic Cancer Linked

A new study funded in part by NIEHS reports novel findings related to the basic biology of pancreatic cancer, confirming that blood type is related to pancreatic cancer. More specifically, people with any blood type other than O are at a slightly increased risk for pancreatic cancer, a relatively rare, but usually fatal cancer.

The team determined ABO genotypes in about 1500 cases and controls from twelve cohorts of participants enrolled in the Pancreatic Cancer Cohort Consortium (PanScan).

These findings are important because they provide some insights into the biology of the disease. Previous research found that normal pancreas cells carry a different pattern of the blood-type antigens on their surface than do pancreatic cancer cells. This suggests that changes in the ABO gene activity may occur as the cells become cancerous, possibly by interfering with the cells' ability to signal and adhere to one another and with the immune system's ability to recognize them as abnormal cells. The researchers point out that the ABO gene could also merely be a marker for other nearby genes that are more directly involved in cancer development.

The association between blood type and pancreatic cancer risk provides a new line of investigation for understanding the mechanisms involved in pancreatic cancer development.

Citation: [Wolpin BM, Kraft P, Gross M, Helzlsouer K, Bueno-de-Mesquita HB, Steplowski E, et al. 2010. Pancreatic cancer risk and ABO blood group alleles: results from the pancreatic cancer cohort consortium. Cancer Res 70\(3\):1015-23.](#)

[Return to Table of Contents](#)

African Ancestry and Asthma

In the first genome-wide association study focused on populations of African descent, a multi-institutional team of researchers identified 3 single nucleotide polymorphisms (SNPs) that are biologically relevant to asthma and may help to explain at least part of the profound disparities in asthma observed in different populations.

Asthma is a biologically complex disease. It is affected by many non-biological issues as well as environmental, social, cultural, and economic factors; however, these factors have not proven to be the cause of the striking ethnic disparities. This study was designed to identify genes that might explain at least part of the racial disparity seen in the incidence of the disease.

Two populations of African descent were included in this study. One group consisted of 935 African-American and control subjects and the other consisted of 929 African Caribbean asthmatics and their family members. The study yielded three highly statistically significant SNPs for genes that are biologically relevant to asthma. Additional studies on groups from the U.K. and Germany did not find the same associations. Similar associations were also not found in four other case-control studies in African Americans.

The authors conclude that additional studies of these three candidate genes are warranted to confirm the possible uniqueness of the observed associations to populations of African descent. Because of the difficulty in finding SNP-for-SNP replication in all of the African populations, they suggest conducting fine-mapping studies around these three genes.

Citation: Mathias RA, Grant AV, Rafaels N, Hand T, Gao L, Vergara C, et al. 2010. A genome-wide association study on African-ancestry populations for asthma. J Allergy Clin Immunol 125(2):336-346.e4.

(Jerry Phelps is a program analyst in the NIEHS Division of Extramural Research and Training.)

[Return to Table of Contents](#)

Intramural Papers of the Month

By Laura Hall and Omari Bandele

- [VEGF Rapidly and Reversibly Downregulates P-glycoprotein Activity in the Blood Brain Barrier](#)
- [Threonine-38 Dephosphorylation is Necessary for Human CAR Activation](#)
- [Pesticide Use Linked to Thyroid Disease Among Women](#)
- [Escherichia coli CysJ Flavin Reductase Detoxifies Mutagenic Nucleobases](#)

VEGF Rapidly and Reversibly Downregulates P-glycoprotein Activity in the Blood Brain Barrier

NIEHS investigators have demonstrated that vascular endothelial growth factor (VEGF) exposure acutely and reversibly downregulates P-glycoprotein (P-gp) transport activity in the rat blood-brain barrier (BBB) *in vitro* and *in vivo* without changing transporter protein expression.

Increased brain expression of VEGF, a protein that stimulates blood vessel growth, is associated with brain injury and disease, as well as dysfunction of the protective BBB. P-gp is a critical efflux transporter in the BBB that plays a major role in protecting the brain against neurotoxicants, but also limits therapeutic drug entry into the brain. These results imply that P-gp activity could be greatly reduced in disease states associated with increased VEGF brain expression.

The study findings indicate that VEGF decreases P-gp activity by signaling through flk-1, a VEGF receptor, and Src kinase, a tyrosine residue phosphorylation enzyme. VEGF also increased Src mediated tyrosine-14 phosphorylation of the membrane scaffolding protein, caveolin-1. This membrane protein may play a role in downregulation of P-gp activity by aiding in internalization of the transporter.

The authors suggest that changing P-gp activity by targeting the BBB VEGF/Src signaling pathway could be a novel strategy to improve brain drug delivery.

Citation: Hawkins BT, Sykes DB, Miller DS. 2010. Rapid, reversible modulation of blood-brain barrier P-glycoprotein transport activity by vascular endothelial growth factor. J Neurosci 30(4):1417-1425.

[Return to Table of Contents](#)

Threonine-38 Dephosphorylation is Necessary for Human CAR Activation

NIEHS scientists have demonstrated that the phosphorylation state of the threonine-38 residue regulates the translocation and activation of human constitutive androgen receptor (CAR). The critical kinase that phosphorylates threonine-38 is protein kinase C, making the phosphorylation part of a signal-mediated mechanism.

CAR is a nuclear receptor that senses drugs, such as phenobarbital, and xenobiotic compounds. These compounds activate CAR, causing it to translocate from the cytoplasm to the nucleus where it binds to DNA and initiates the expression of many genes involved with metabolism and excretion. In the liver, CAR plays an important role in drug, glucose, fatty acid, cholic acid, and bilirubin metabolism.

Structural modeling located the threonine-38 in the CAR DNA binding domain to the C-terminal portion of the alpha-helix spanning from residues 29-42 in the first zinc finger and the region between the zinc fingers. Study results show that phosphorylation at threonine-38 may destabilize the helix, which keeps CAR in the cytoplasm and also prevents DNA binding.

The investigators demonstrated that in the mouse liver, phenobarbital dephosphorylated CAR in the cytoplasm before translocating CAR into the nucleus. For pathophysiological conditions such as diabetes and high fat diets that naturally activate CAR, threonine-38 phosphorylation/dephosphorylation could represent a therapeutic target.

Citation: [Mutoh S, Osabe M, Inoue K, Moore R, Pedersen L, Perera L, et al. 2009. Dephosphorylation of threonine 38 is required for nuclear translocation and activation of human xenobiotic receptor CAR \(NR1I3\). J Biol Chem 284\(50\):34785-34792.](#)

[Return to Table of Contents](#)

Pesticide Use Linked to Thyroid Disease Among Women

A collaborative study involving researchers from NIEHS and the University of Nebraska Medical Center has provided evidence that links pesticide exposure to the development of thyroid disease among female spouses of pesticide applicators.

In this study, published in the American Journal of Epidemiology, Whitney Goldner, M.D., and colleagues examined the association between 5 organochlorine insecticides and 39 other pesticides — including herbicides, fungicides, and fumigants — and thyroid disease in 16,500 spouses enrolled in the Agricultural Health Study. The prevalence of self-reported clinically diagnosed thyroid disease was 12.5 percent. The prevalence of hypothyroidism (underactive thyroid) and hyperthyroidism (overactive thyroid), in the spouses, was 6.9 and 2.1, respectively.

The authors compared the pesticide use histories of women with thyroid disease to those of women who did not report any thyroid problems. They found an association between developing hypothyroidism and overall use of organochlorine insecticides and fungicides. Specifically, the research revealed associations between hypothyroidism and the organochlorine insecticide chlordane, the fungicides benomyl and maneb/mancozeb, and the herbicide paraquat. The researchers also found an elevated risk of hyperthyroidism with exposure to maneb/mancozeb.

These novel findings illustrate that environmental exposure to pesticides should be considered potential risk factors for thyroid disease.

Citation: [Goldner WS](#), [Sandler DP](#), [Yu F](#), [Hoppin JA](#), [Kamel F](#), and [LeVan TD](#). 2010. Pesticide use and thyroid disease among women in the Agricultural Health Study. *Am J Epidemiol* 171(4):455-464.

[Return to Table of Contents](#)

***Escherichia coli* CysJ Flavin Reductase Detoxifies Mutagenic Nucleobases**

Researchers from the NIEHS have identified CysJ flavin reductase as an essential component of a novel *Escherichia coli* (*E. coli*) detoxification system, which inactivates 6-*N*-hydroxylaminopurine (HAP) — a highly mutagenic DNA base analog. The study also illustrates that this activity is distinct from its contribution to the sulfite reductase complex (CysJI).

Roel Schaaper, Ph.D., and colleagues previously demonstrated that HAP-resistance in *E. coli* depends upon two newly described proteins, Ycbx and YiiM, which utilize Molybdenum Cofactor (MoCo) to reduce N-hydroxylated compounds to non-toxic forms. In their current work, published in the *Journal of Bacteriology*, the investigators show that CysJ is a specific partner of YcbX in *E. coli* and mediates HAP resistance through its oxidoreductase activity. Schaaper proposes that CysJ provides electrons to YcbX, which ultimately completes the reduction of HAP to non-mutagenic adenine.

The group further emphasized the close interaction between CysJ and YcbX during HAP detoxification by characterizing a Cys-YcbX “hybrid” from two bacterial species that can complement a double deficiency of these proteins in *E. coli*.

Citation: [Kozmin SG](#), [Wang J](#), [Schaaper RM](#). 2010. A role for CysJ flavin reductase in molybdenum cofactor-dependent resistance of *Escherichia coli* to 6-*N*-hydroxylaminopurine. *J Bacteriol*. January 29 doi:10.1128/JB.01438-09 [Epub ahead of print].

(Laura Hall is a biologist in the NIEHS Laboratory of Pharmacology currently on detail as a writer for the Environmental Factor. Omari Bandele, Ph.D., is a postdoctoral fellow in the NIEHS Laboratory of Molecular Genetics Environmental Genomics Group.)

[Return to Table of Contents](#)

Inside the Institute

A Call for National Lab Day Volunteers

By Eddy Ball

NIH Director Francis Collins, M.D., Ph.D., recently announced that he will celebrate National Lab Day (NLD) on the front lines of science education in a Washington, D.C. high school. In his [personal message to extramural scientists](#), he encouraged participation by other NIH scientists as a way to “bring scientists like you together with K-12 teachers and students across the country for a day of hands-on learning.”

Although May 5 is designated as the official [NLD](#), Collins and event organizers emphasize that NLD “is more than a day — it’s a movement ... a national barn-raising for hands-on learning” that has already begun across the nation. The NLD website offers a way for scientists to volunteer their talents and for science teachers everywhere to post project requests and find resources to match their needs (watch [video](#) at White House Web site).

Collins asked scientists to check out resources at the NIH Science Education Nation [Home Page](#) and sign up to help schools in their communities improve science achievement. Several teachers in the Durham area have already posted requests, and more Triangle area educators are sure to sign up as publicity about NLD grows.

In his message, Collins pointed to the country’s dismal ranking in terms of 15 year olds’ science achievement — number 29 out of 57 countries — and the need for young people to develop effective problem-solving skills to function as responsible adults. “Not only is the future of biomedical research in danger,” he explained, “but the future health of our economy depends on a workforce with quantitative skills in math and science.”

NLD is a non-profit organization sponsored by the National Science Teachers Association, American Chemical Society (ACS), MacArthur Foundation, Jack D. Hidary Foundation, NIH, and National Science Foundation.



In his NIH-wide announcement March 11, Collins wrote that he looks forward to “doing hands-on science and talking about what makes science and discovery so cool to me.” (Photo courtesy of NIH)



[Return to Table of Contents](#)

Exploring the History of Women in Science

By Eddy Ball

The NIH Women's History Month Celebration featured two prominent NIH women scientists addressing the topic of "Writing Women into the History of Science" on March 17. Elizabeth Fee, Ph.D., and Vivian Pinn, M.D., were the keynote speakers at the event, which was webcast from Wilson Hall on the NIH Campus in Bethesda and archived [online](#).

[Fee](#) is the chief of the History of Medicine Division at the National Library of Medicine (NLM), and [Pinn](#) is director of the Office of Research on Women's Health (ORWH) and NIH associate director for Research on Women's Health (watch [video](#) about Pinn).

Reflections on the early days

In her talk, Fee reviewed the contributions of women to the development of science and looked at efforts to inscribe them back into the history they were instrumental in shaping. She launched her presentation with an account of her own experience when she told her parents she wanted to study biochemistry at Cambridge.

Her parents, Fee said, were not supportive initially, telling her instead to study cooking and home economics to become a better wife and mother. Their attitude was a hangover of some of the earlier prejudices — "Women were said to have small brains but nimble fingers" — that kept women in the role of assistants and denied them recognition for their significant contributions to scientific advances.

Fee traced that theme through the 19th and 20th centuries. Women advanced during the times of war, she explained, only to lose ground afterwards, until breakthroughs were made possible by the women's rights movement. It was then, she noted, that historians began the gradual process of "changing the face of science and celebrating the contributions of women in science" — the theme of a new multimedia [NLM exhibit](#).

Focus on women at NIH

Following Fee's overview, Pinn brought the program home for NIH women, by recalling the environment at NIH when she began her duties in ORWH in 1991 and discussing recent and current initiatives to improve women's experiences in the workplace. She pointed to some of the female standard bearers of the past 20 years, such as [Bernadine Healy, M.D.](#), the only woman to head NIH, and [Ruth Kirschstein, M.D.](#), the first director of an institute or center (IC) at NIH.



As director of ORWH, Pinn has been proactive in advocating for women's health and for their advancement in scientific and administrative fields at NIH and elsewhere. (Photo courtesy of NIH)



Alving was appointed director of NCRR by former NIH Director Elias Zerhouni, M.D., in 2007. In her remarks, Pinn credited Zerhouni for his support of women at NIH and said that NIH Director Francis Collins, M.D., Ph.D., has demonstrated his support for ongoing initiatives. (Photo courtesy of NIH)

Pinn surveyed women's accomplishments in several NIH initiatives and publications with an impressive catalogue of women in top leadership positions, including most recently the appointment of Linda Birnbaum, Ph.D., as NIEHS/NTP director. "What a change from when I came and there was one institute director and one center director," Pinn observed.

In her closing remarks, National Center for Research Resources Director [Barbara Alving, M.D.](#), approached the topic in terms of workplace diversity. Alving acknowledged the continuing gap between women and men in terms of retention and career advancement despite important gains in terms of the percentage of women in training for careers in science, technology, engineering, and mathematics, as she commented on the leading role of NIH in working toward greater equality.

Looking toward the future, Alvin emphasized the importance of inclusion. "We can [all] be minorities in so many different ways," she said, pointing to demographic trends and projections. Alving also underscored the continuing need for expanded childcare services at NIH, which she said benefits men as fathers, as well as women as mothers.

[Return to Table of Contents](#)

Health and Fitness Week Begins May 3

By Laura Hall

During the first week in May, the annual NIEHS Health and Fitness Week will offer staff a bounty of fun and healthy activities. The theme of this year's event is "Supporting a Healthy Lifestyle Through Nutrition and Weight Management."

Festivities begin the last week in April as participants sign up for the Taking Steps to Your Health Contest. Teams of three employees will be tracking their steps for a week using pedometers and then submit their total number of steps taken at the end of Fitness Week. Fitness Room Manager Stephanie Bullock-Allen will assign people to teams and give out the pedometers.

The informative seminars, "Quick Healthy Meals" on Monday, May 3, and "Portion Distortion — Are You on a Sugar High?" on Wednesday will discuss easy ways to maintain a healthy diet.

Throughout the week, there will be contests in basketball, football throws, fitness, and table tennis, as well as Wii games, a jump rope demonstration, a Tai Chi demonstration, and a golf outing — an off-campus event that requires participants to take annual leave. The annual "Rogathon" 5K run and a two mile nature walk will take place on Wednesday.

Participants can exercise without competing in the Power Yoga class and the Cardio Dance Party. Bike-to-Work events are scheduled throughout the month of May. Also, for those who just want to relax, the ever popular chair massages are available by appointment on Wednesday.



Former Postdoctoral Fellow Jennifer Adair, Ph.D., was one of many NIEHS runners who have taken advantage of an opportunity to compete during past Health and Fitness weeks. (Photo courtesy of Steve McCaw)

Organizers plan to distribute flyers, posters, and e-mails later this month with schedules and sign-up information. The Health and Fitness Week event is sponsored by the Office of Management Health and Fitness organizing committee.

(Laura Hall is a biologist in the NIEHS Laboratory of Toxicology and Pharmacology currently on detail as a writer for the Environmental Factor.)



Gordon Caviness went for the goal against the rival team in the annual basketball tournament two years ago. (Photo courtesy of Steve McCaw)



A playful Heather Henry couldn't resist showing off for the camera during Bike-to-Work Month in 2008. (Photo courtesy of Steve McCaw)

[Return to Table of Contents](#)

EPA Earth Day Extravaganza to Welcome NIEHS Staff

By Laura Hall

Organizers of Earth Day events at the U.S. Environmental Protection Agency (EPA) have invited NIEHS staff to join with them in celebrating the 40-year anniversary of Earth Day with special events April 20-22.

Dick Sloane and Danica Andrews, co-chairs of the NIEHS Environmental Awareness Advisory Committee (EAAC), said that the committee decided to forgo an Earth Day event this year at NIEHS. "EPA is planning a massive 'blow out' Earth Week event and the entire NIEHS family has been invited to attend," said Sloane. The EAAC, which plans and sponsors the annual NIEHS Earth Day event, will instead sponsor a series of "Earth" activities throughout the month of May beginning with Health and Fitness Week May 3 (see [story](#)).

Events include two talks by notable environmentalists and a number of green fun and educational events:

Hunter Lovins, dubbed a "green business icon" by Newsweek magazine in 2009, will speak about "The Business Case for Climate Protection" on April 21 at 10:00 a.m. Lovins is a well-known author and

consultant with expertise in sustainability, climate change, and what she calls “natural capitalism” — an initiative for making the Earth’s resources a strategic business priority.

A ribbon-cutting ceremony celebrating the Duke Energy installment of solar photovoltaic panels on top of the roof of the First Environments Early Learning Center — the NIEHS and EPA co-sponsored childcare facility — will take place April 22 on the EPA plaza beginning at 10:00 a.m. The ceremony will be followed with a keynote address, “Visionary Environmental Business Leader and Advocate,” by Robert F. Kennedy Jr.

On April 21, the fun begins with the 5K EPA-RTP Fun Run and Walk at 9:00 a.m. at the EPA Building C plaza. Afterwards, the event will feature two videos — “A Sense of Wonder,” about Rachel Carson and her efforts to protect the environment, and “Air Science 40,” about the past 40 years of air quality research and regulations.

Several nature walks and talks, a butterfly garden design talk by North Carolina Botanical Garden staff, and a green vendor fair are scheduled as well.

The EAAC will send out emails with the entire schedule and any necessary sign up instructions later in April.

(Laura Hall is a biologist in the NIEHS Laboratory of Toxicology and Pharmacology currently on detail as a writer for the Environmental Factor.)

[Return to Table of Contents](#)



Last year, Andrews welcomed employees to the Earth Week kick off at NIEHS. This year she'll be on hand at the EPA-hosted celebration of the 40th anniversary of Earth Day. (Photo courtesy of Steve McCaw)



NIEHS
National Institute of
Environmental Health Sciences

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

The e-Factor, which is produced by the Office of Communications and Public Liaison, is the staff newsletter at the National Institute of Environmental Health Sciences. It is published as a communication service to NIEHS employees. We welcome your comments and suggestions. The content is not copyrighted. It can be downloaded and reprinted without permission. If you are an editor who wishes to use our material in your publication, we ask that you send us a copy for our records.

- Director of Communications: [Christine Bruske](#)
- Writer-Editor: [Eddy Ball](#)
- Science Editor: [Robin Arnette](#)